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SYSTOLIC BLOOD PRESSURES IN YOUNG MEN

INCLUDING A SPECIAL STUDY OF THOSE WITH HYPERTENSION *

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MINNEAPOLIS

When considering the subject of hypertension, one is impressed with the indefiniteness of our knowledge. Some of the sequelae of hypertension have long been recognized and life insurance companies have been emphasizing the importance of hypertension, even though unaccompanied by other symptoms. Fahr [1] estimates that approximately 50,000 persons in the United States die each year from "hypertension heart," and that probably an equal number of deaths reported as apoplexy and Bright's disease are actually the result of hypertension. This would mean that hypertension ranks foremost among the causes of death in this country.[2] But even with the general realization as to the importance of the condition, we are unable as yet to draw a sharp line between normal blood pressure and low grade hypertension, and we lack definite information concerning the age at which hypertension makes its first appearance.

Alvarez,[3] in an attempt to determine what constitutes normal blood pressure in young persons, has made some very excellent studies of the blood pressure records of freshmen students at the University of California. The readings were made over a period of four years and include records of 6,000 men and 8,934 women. He found that 45 per cent. of the men had systolic pressures exceeding 130 mm., and 22 per cent. had pressures exceeding 140 mm.; that about 12 per cent. of the women had pressures exceeding 130 mm. and about 2 per cent. had pressures exceeding 140 mm. He found that the average pressure for both men and

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1. Fahr, G. E.: Hypertension Heart, J. A. M. A. **80**:981 (April 7) 1923.

2. Mortality Statistics, U. S. Census Bureau, Washington, Government Printing Office, 1922.

3. Alvarez, W. C.; Wulzen, R., and Mahoney, L. J.: Blood Pressures in Fifteen Thousand University Freshmen, Arch. Int. Med. **32**:17 (July 15) 1923.

women tends to drop during the first years of adult life. These figures seemed surprisingly high and so have been compared with the blood pressure readings of the freshmen men examined at the University of Minnesota. The examinations of the women students have been made under somewhat different conditions and so will be studied separately.

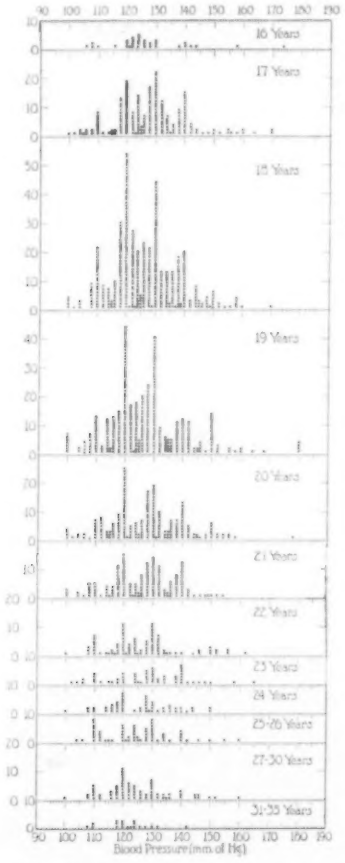

Fig. 1.—Actual systolic blood pressure readings of 1922 group, each dot representing one case.

TECHNIC EMPLOYED

Every student who enters the University of Minnesota is required to have a complete physical examination at the time of his matriculation. Blood pressure readings are taken as a matter of routine as part of this examination. The auscultatory method is used with mercury manometers or recently standardized aneroid instruments. The technic

employed is described by Schneider [4] in connection with his cardiovascular efficiency test. The student reclines on a bed for several minutes before the blood pressure reading is taken. If on the first reading the systolic pressure is 140 mm. or more, the examiner passes on to other

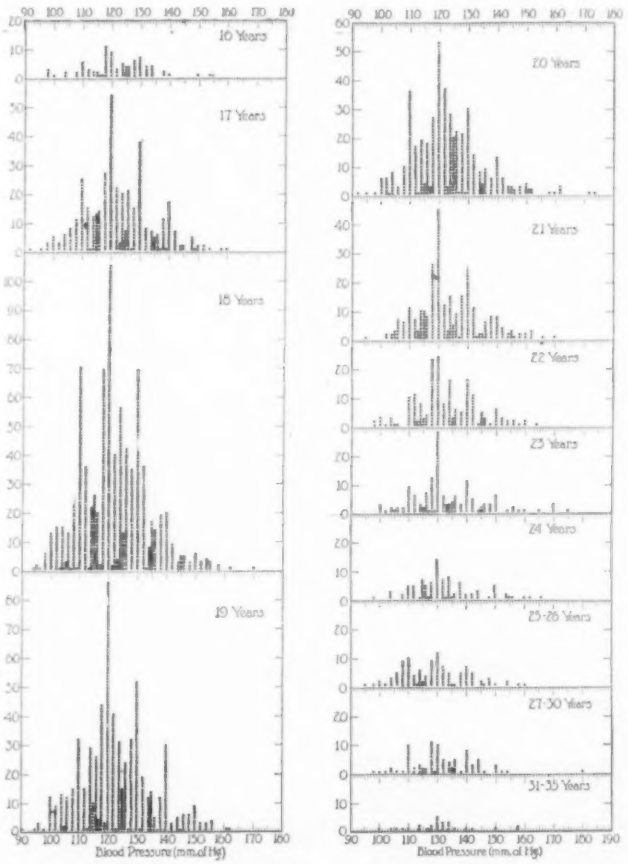

Fig. 2.—Actual systolic blood pressure readings of 1923-1924 group, each dot representing one case.

students and returns to take a second reading in five or ten minutes. This reading is then recorded. In the 1922 examinations second readings were not made, the original readings being recorded. For this reason the students examined in 1922 are studied as a separate group from those examined in 1923 and 1924.

4. Schneider, E. C.: Cardiovascular Rating as a Measure of Physical Fatigue and Efficiency, J. A. M. A. **74**:1501 (May 29) 1920.

TABLE 1.—*Total Blood Pressures in Men Students According to Age Groups for 1922*

Pressure	Ages 16	17	18	19	20	21	22	23	24	25-26	27-30	31-35	36-40	Total	Percentages Actual	Cumulative	Pressure
90-94	..	..	..	..	..	..	..	..	..	..	..	..	..	..	.....	.....	90-94
95-99	..	..	..	..	..	..	..	..	..	..	..	..	..	..	.....	.....	95-99
100-104	..	4	8	9	7	5	1	2	1	1	1	..	..	39	2.31	2.31	100-104
105-109	3	5	10	11	3	6	3	2	2	1	2	1	1	50	2.96	5.28	105-109
110-114	1	10	37	28	18	10	9	5	4	13	7	2	1	145	8.65	13.87	110-114
115-119	1	17	43	30	18	16	8	4	7	2	8	3	..	157	9.31	23.19	115-119
120-124	13	43	103	80	37	26	12	8	8	15	22	8	1	386	22.89	46.08	120-124
125-129	5	27	51	49	26	22	8	7	9	8	5	2	..	219	12.98	59.07	125-129
130-134	3	41	70	55	33	28	20	11	7	12	11	2	2	295	17.49	76.57	130-134
135-139	1	14	37	21	17	16	3	3	5	1	3	..	..	121	7.23	83.74	135-139
140-144	4	21	31	25	20	16	2	9	5	5	3	1	..	142	8.43	92.17	140-144
145-149	..	2	10	7	5	3	2	2	..	1	4	..	1	37	2.19	94.36	145-149
150-154	..	3	9	17	10	3	5	1	2	1	2	..	..	53	3.14	97.51	150-154
155-159	1	4	5	3	3	..	2	1	..	1	..	..	..	20	1.17	98.69	155-159
160-164	..	3	1	3	..	..	1	..	..	1	1	..	..	10	0.58	99.28	160-164
165-169	..	..	..	1	..	..	..	1	..	..	..	..	..	2	0.12	99.40	165-169
170-174	1	2	1	..	..	..	..	..	..	..	..	..	..	4	0.24	99.64	170-174
175-179	..	..	..	4	..	..	..	..	..	..	..	..	..	1	0.06	99.70	175-179
180-184	..	..	..	..	1	..	..	..	..	..	..	..	..	4	0.24	99.94	180-184
185-189	..	..	..	..	..	..	..	..	..	..	..	..	..	..	.....	.....	185-189
190-194	..	..	..	..	..	..	..	..	..	..	..	..	..	..	.....	.....	190-194
195-199	..	..	..	..	..	..	..	..	..	..	..	..	..	..	.....	.....	195-199
200-204	..	..	1	..	..	..	..	..	..	..	..	..	..	1	0.06	100.00	200-204
Total	33	196	417	343	198	151	86	56	50	62	69	19	6	1,686			
Percentage over 130 mm.	30.3	45.9	39.5	39.6	44.9	43.7	40.6	50.0	38.0	35.4	34.7	15.7	50.0	40.9			
Percentage over 140 mm.	18.1	16.8	13.8	17.4	19.6	14.5	13.9	25.0	14.0	14.5	14.4	5.2	16.6	16.2			
Mode (actual)	124	130	120	120	120	120	120 130	140	120	110 130	120	118 120 124	130	120			
Mode calculated	117.8	127.6	121.8	123.4	124.4	122.0	119.0	127.0	130.8	122.0	115.4	119.2	120.2	124.2			
Mean	127.1	128.4	126.6	127.3	127.1	126.5	126.5	128.5	126.2	125.0	125.3	121.9	123.8	126.9			
Median	124	128	125	126	128	128	124	128	128	124	122	121	125	126			
Standard deviation	13.4	12.1	11.9	13.4	12.8	11.1	12.3	13.3	11.1	11.9	11.5	7.9	12.8	12.4			
Coefficient of variation	9.4	10.6	10.6	9.4	9.9	11.3	10.2	9.6	11.3	10.5	10.9	15.4	9.6	10.2			
Measure of skewness	0.69	0.99	0.40	0.29	0.21	0.40	0.60	0.11	0.48	0.25	0.86	0.34	0.28	0.21			
Probable error	9.04	8.16	8.03	9.04	8.63	7.48	8.30	8.97	7.49	8.03	7.76	5.33	8.63	8.36			
Unreliability (standard deviation) of the mean	2.35	0.85	0.58	0.72	0.90	0.90	1.21	1.78	1.56	1.50	1.38	1.79	5.12	0.30			
Probable error of the mean	1.59	0.57	0.39	0.49	0.61	0.61	0.82	1.20	1.05	1.01	0.93	1.21	3.45	0.20			

TABLE 2.—*Total Blood Pressures in Men Students According to Age Groups for 1923-1924*

Pressure	Ages 16	17	18	19	20	21	22	23	24	25-26	27-30	31-35	36-40	Total	Percentages— Actual	Cumulative	Pressure
90-94	..	1	1	1	1	..	..	..	..	..	..	..	..	4	0.11	0.11	90-94
95-99	3	4	9	5	2	1	2	..	1	2	1	..	..	30	0.87	0.98	95-99
100-104	3	14	45	34	21	4	7	6	3	6	4	2	..	149	4.34	5.34	100-104
105-109	2	19	44	29	13	16	2	5	2	14	2	2	..	150	4.36	9.71	105-109
110-114	11	53	129	77	74	31	31	18	11	21	15	3	3	477	13.88	23.57	110-114
115-119	15	55	117	87	52	44	30	23	19	15	16	3	2	478	13.90	37.48	115-119
120-124	17	99	208	159	122	75	52	40	30	24	19	11	3	850	24.70	62.48	120-124
125-129	14	44	90	72	65	30	14	13	9	7	8	1	..	367	10.68	73.16	125-129
130-134	15	53	117	84	52	39	28	17	7	12	16	2	..	442	12.86	86.03	130-134
135-139	2	24	50	32	19	16	9	8	1	6	1	..	..	168	4.88	90.92	135-139
140-144	1	26	32	38	22	14	11	7	7	3	5	1	..	167	4.86	95.78	140-144
145-149	..	8	13	13	8	6	3	3	2	1	..	2	..	59	1.71	97.49	145-149
150-154	3	5	13	15	6	5	3	1	2	1	..	..	..	54	1.57	99.06	150-154
155-159	1	1	5	4	1	1	..	1	1	..	..	..	..	15	0.43	99.21	155-159
160-164	..	1	1	2	4	1	..	3	..	..	..	..	..	12	0.34	99.85	160-164
165-169	..	..	..	..	..	..	..	1	..	..	..	..	..	1	0.03	99.88	165-169
170-174	..	..	1	..	2	..	..	..	..	..	1	..	..	4	0.11	100.00	170-174
175-179	..	..	..	..	..	..	..	..	..	..	..	..	..	..			
180-184	..	..	..	..	..	..	..	..	..	..	..	..	..	..			
185-189	..	..	..	..	..	..	..	..	..	..	..	..	..	..			
Total	87	407	875	652	464	283	192	146	95	112	88	27	8	3,436			
Percentage over 130 mm.	25.2	28.9	26.5	28.8	24.5	28.9	28.1	28.0	21.0	20.5	26.1	18.5	....	26.4			
Percentage over 140 mm.	5.7	10.0	7.4	11.0	9.2	9.5	8.8	10.9	12.6	4.4	6.8	11.1	....	9.0			
Mode (actual)	118	120	120	120	120	120	120	120	120	120	118	120	110 120	120			
Mode (calculated)	115.4	120.4	116.4	120.0	117.8	113.2	114.8	119.4	114.8	116.0	117.0	117.8	114.0	120.6			
Mean	122.3	122.8	121.8	123.0	124.1	123.4	122.6	123.3	122.6	119.0	121.5	121.1	115.5	122.7			
Median	120	122	120	122	122	120	120	122	120	118	120	120	116	122			
Standard deviation	11.4	11.4	11.5	11.6	11.3	10.8	10.4	12.2	11.1	11.0	10.6	11.3	4.4	11.3			
Coefficient of variation	10.7	10.7	10.5	10.6	10.9	11.4	10.8	10.1	11.0	10.8	11.4	10.7	26.2	10.8			
Measure of skewness	0.60	0.21	0.47	0.25	0.55	0.94	0.75	0.32	0.70	0.27	0.42	0.29	0.34	0.18			
Probable error	7.69	7.69	7.76	7.82	7.62	7.28	7.01	8.22	7.49	7.42	7.15	7.62	2.97	7.62			
Unreliability (standard deviation) of the mean	1.22	0.56	0.39	0.45	0.52	0.64	0.74	1.00	1.14	1.03	1.12	2.17	1.57	0.19			
Probable error of the mean	0.82	0.38	0.26	0.30	0.35	0.43	0.50	0.67	0.77	0.69	0.76	1.46	1.06	0.13			

STATISTICAL ANALYSIS

The blood pressure records were tabulated and analyzed according to various statistical methods to test their reliability and to show tendencies in the groups. In the 1922 group, there were 1,686 students and in the 1923-1924 groups, 3,436 students, making a total of 5,122 men in the entire series.

Fig. 3.—Average blood pressure of each age group and of the total in each of the three calendar years, 1922, 1923 and 1924.

Figure 1 is the tabulation of the actual blood pressure readings according to age for the 1922 group. Figure 2 is a similar tabulation for the 1923-1924 group. These charts show the great tendency of examiners to read to even numbers and particularly to tens. In these 5,000 examinations there were almost no pressures recorded as 119 or 121, and less recorded as 125 than as 124 and 126.

TABULATION OF TOTALS

The total number of students whose blood pressures were used in this study was 5,122. Of these, 1,686 entered the University in 1922; 1,826 in 1923, and 1,610 in 1924. Because of the slight differences in technic already described, the 1922 group has been tabulated separately from the 1923 and 1924 groups. In his studies Alvarez has arranged the blood pressures in such groups as 100-104, 105-109, etc.[3] Tables 1 and 2 show our readings arranged in the same manner. As can be seen even from these tables, the chief grouping of pressures is between 110 and 130. In the 1922 group, the four students 19 years of age with pressure between 180 and 184 strike as unusual. It seems probable, however, that the occurrence of all these in one age group is a coincidence. One had hyperthyroidism, one aortic regurgitation, one transient hypertension and one persistent hypertension.

AVERAGES FOR VARIOUS YEARS

Figure 3 shows the average pressure of each age group for each of the three years, 1922, 1923 and 1924. These curves are quite regular until the groups of 25 years and above are reached. In these higher ages, the averages become lower but the groups are so small that these figures probably are not reliable. The curve for 1922 is persistently the highest and the one for 1923 persistently the lowest. The higher pressures recorded in 1922 may be due to the difference in technic, but there is no such explanation for the height of the 1924 curve. This seems to be some evidence of the tendency noted by Alverez for blood pressures to vary somewhat in different calendar years, a point that merits further study.

MEASURES OF CENTRAL TENDENCY

The arithmetical mean, in other words the average pressure, is shown graphically in Figure 3 and has been discussed in the preceding paragraph. The mean for the entire 1922 group is 126.9 mm. and for the 1923-1924 group 122.7 mm.

The calculation of the unreliability (variation) of the mean, which Alvarez calls the standard deviation of the mean, was made according to Rugg's formula.[5]

The most probable error of the mean then was calculated from this standard deviation.[6] In practically all the age groups this most probable error is very low.

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5. $\sigma m = \frac{\sigma \text{ deviation}}{\sqrt{N}}$; that is, the standard deviation divided by the square of the number of cases. Rugg, H. O.: Statistical Methods Applied to Education, New York, Houghton Mifflin Company, 1917, p. 227.

6. The most probable error equals the standard deviation multiplied by 0.6745.

The actual (observed) mode is the pressure occurring most frequently in any group. For the different age groups in the 1922 examinations the mode varies considerably, but it is 120 mm. for most ages (Fig. 1). In the more dependable 1923-1924 examinations, the mode varies only between 118 and 120 mm., 120 mm. being by far the most common (Fig. 2).

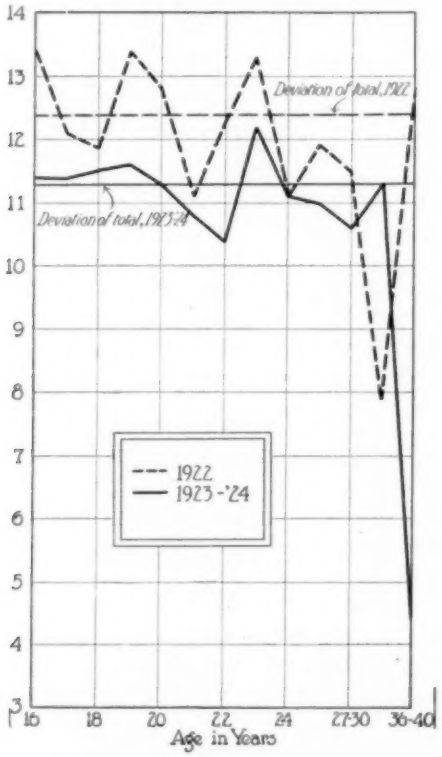

Fig. 4.—Standard deviation, as given in Table 1, for each age group.

The calculated modes have been computed according to Pearson's method.[7] These calculated modes for each age group are lower in all years than the observed modes.

The median pressure is the middle figure, that is, the pressure that has just as many readings above it as below it. In 1922 the median varied between 121 and 128, with the median of the total 126. In the 1923-1924 group, the variation was between 116 and 122, with the median of the total 122.

7. The calculated mode equals the mean — 3 (mean — median).

MEASURES OF VARIABILITY

Some ideas as to the reliability of statistical data can be obtained by computing the standard deviation, the coefficient of variation, and the most probable error.[8]

The variability of the standard deviation and the coefficient of variation in the different age groups is shown in Tables 1 and 2 and Figures 4 and 5. The smallness of these measures and the regularity of the graphs shows that statistically the figures are reliable except in the higher age groups; in these the totals are too small to be of value.

SKEWNESS OF THE CURVES

Any curves drawn through the high points of the individual readings, as shown in Figures 1 and 2, would be extremely irregular and very confusing. Furthermore, the small differences in pressure that would make such curves irregular are of so little clinical significance that the curves would be misleading. A better idea can be obtained from percentage frequency diagrams shown in Figures 6, 7, 8 and 9. In preparing these charts, groups of ten were used because most physicians think of blood pressures as being "around 120 mm., around 130 mm., around 140 mm.," etc.; and the readings most frequently recorded, i. e., 110 mm., 120 mm., 130 mm., 140 mm., etc., were used as the midpoints of the groups. The figures in each group were then reduced to percentages and plotted.

These groups were preferred to the ones given by Alvarez because, if one uses groups such as 120-124, 130-134, etc., with high points, such as 120 and 130, at one extreme (Figs. 1 and 2), and then assumes that the data are evenly distributed within the groups, the conclusions will not be absolutely accurate. If groups of five are preferred, they should be from 118 to 122, from 123 to 127, etc.

In the 1922 examinations, the percentage of pressures between 115 and 124 mm. is highest in six of the age groups, and the percentage between 125 and 134 mm. is highest in seven of the groups. Of the

8. The standard deviation was calculated according to the formula

$$S\ D = \sqrt{\frac{\Sigma d^2 - (A_T - A_E)^2}{N}}$$

Σ = Number of cases having each pressure.
d = Deviation of the pressure from the median of the group.
N = Total number of cases in the group.
A_T = True average.
A_E = Even average used in calculating.

The coefficient of variation equals the mean divided by the standard deviation, and the most probable error equals the standard deviation multiplied by 0.6745.

entire class, 34 per cent. had pressures between 115 and 124 mm. and 31 per cent. between 125 and 134 mm. In the 1923-1924 group, however, the percentage with pressures between 115 and 124 mm. is highest for all ages and the percentage between 125 and 134 mm. is second in all but two of the age groups. The distributions for the various ages in 1923-1924 are very similar. All of them, of course, are skewed toward the high pressures, the lowest pressure recorded being 90 mm., 30 mm.

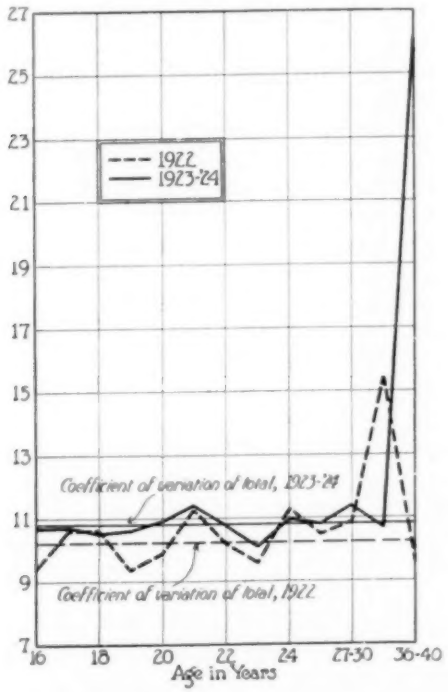

Fig. 5.—Coefficient of variation, as given in Table 1, for each age group.

below the mode, while the upper limits are from two to three times as far removed from the mode.

The measure of skewness was calculated according to Pearson's method.[9] This measure is higher for most ages than is recorded by Alvarez, but with the lower modes in our series, our curves naturally would be more skewed.

9. The measure of skewness is obtained by dividing the difference between the mean and the mode by the standard deviation.

SUMMATION CURVES

The summation curves (Fig. 10, 11 and 12) have been plotted from the percentages shown in Figures 6, 7, 8 and 9. The first point on each curve was obtained by taking the percentage of pressures between 85 and 94; the second point, by adding to this figure the percentage between 95

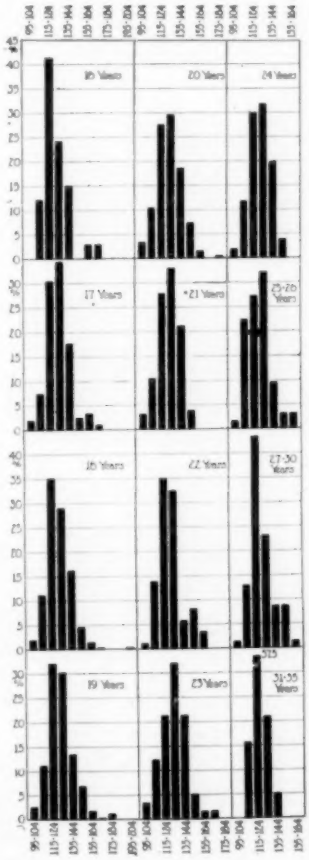

Fig. 6.—Percentage frequency of various pressure groups of 10 mm. for each age in 1922.

and 104; the third point by adding to the sum of the first two the percentage between 105 and 114, and so on. Consequently, the numbers to the left of any perpendicular line represent the percentage of cases below the pressure represented by that line, while the numbers to the right of the perpendicular line represent the percentage of cases

above that pressure. These curves were drawn through the points thus obtained without smoothing. Fifty per cent. on such a graph represents the median. The skewness of the curves toward the higher pressures is clearly shown. These figures also show at a glance the very slight variation in the pressure curves of the different age groups, and the small percentages with high pressures.

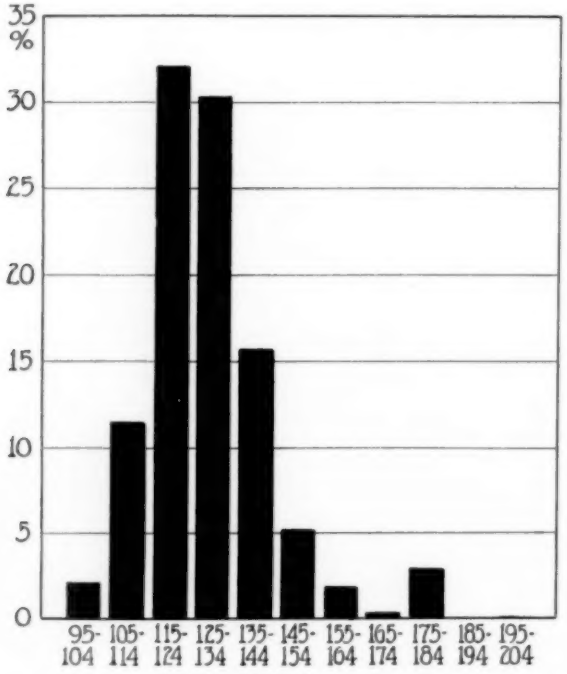

Fig. 7.—Percentage frequency of various pressure groups of 10 mm. for total 1922 group.

PERCENTAGE OF HYPERTENSION

It is generally believed that a persistent systolic blood pressure of 140 mm. or more is abnormal in young persons, and many feel that even 130 is beyond the upper limit of normality. In the 1922 group, 16.2 per cent. had pressures of 140 or more; and 40.9 per cent. pressures of 130 or more. In the more carefully examined 1923-1924 group, only 9 per cent. had pressures over 140 and 26.4 per cent. over 130. These percentages are considerably lower than the ones given by Alvarez, viz., 22 per cent. exceeding 140 and 45 per cent. exceeding 130. In our 1922 group, 1.3 per cent. had pressures of 160 mm. or more and 0.6 per cent.,

of 170 mm. or more; in the 1923-1924 group only 0.5 per cent. had pressures of 160 mm. or more and 0.1 per cent. of 170 mm. or more. The incidence of hypertension, as shown in Figure 13, varies but little for the different age groups, and there is no general tendency, as Alvarez found, for the pressures to be higher in the younger age groups.

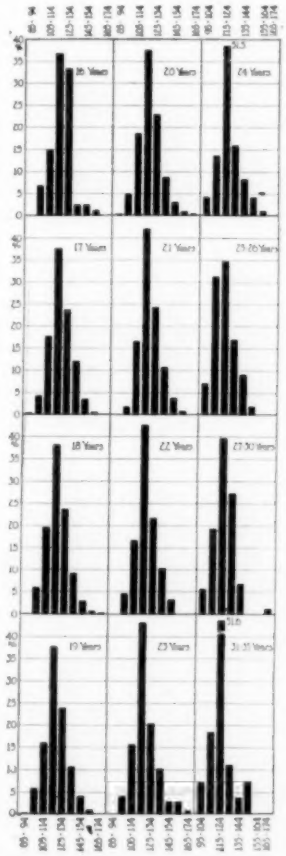

Fig. 8.—Percentage frequency of various pressure groups of 10 mm. for each age in 1923-1924.

REEXAMINATION OF STUDENTS WITH HYPERTENSION

After noting the rather high incidence of hypertension as recorded on the 1922 and 1923 examinations, an attempt was made to obtain some information as to the significance of these findings. With this in mind each student whose systolic pressure was recorded as being 140 mm. or

more was requested to report for reexamination. No compulsion was used to bring these students back, and no attempt was made to check on those who had left the university. Out of a total of 389 who were recorded as having this degree of hypertension, 209, or 53.7 per cent., were reexamined. Some were reexamined only once, others two, three or four times, the average number of reexaminations being 1.7.

TABLE 3.—*Summary of Reexamination of Students Who on First Examination Had Systolic Pressures of 140 Mm. or More*

	Total Reexamined		Secondary Hypertension		Primary Hypertension							
					Transient		Intermittent		Persistent		Total	
Age	No.	Per Cent.*	No.	Per Cent.*	No.	Per Cent.*	No.	Per Cent.*	No.	Per Cent.*	No.	Per Cent.*
16.....	8	18.6	3	7.0	3	7.0	1	2.3	1	2.3	5	11.6
17.....	29	13.0	3	1.3	15	6.8	6	2.6	5	2.3	26	11.7
18.....	53	11.5	1	0.2	30	6.5	13	2.8	9	1.9	52	11.2
19.....	43	11.7	5	1.4	23	6.2	12	3.3	3	0.8	38	10.3
20.....	15	6.4	2	0.9	6	2.6	5	2.1	2	0.9	13	5.6
21.....	18	11.5	0	0.0	7	4.5	5	3.2	6	3.8	18	11.5
22.....	10	9.2	0	0.0	4	3.7	3	2.8	3	2.8	10	9.2
23.....	9	11.8	2	2.6	4	5.3	3	4.0	0	0.0	7	9.3
24.....	7	11.9	0	0.0	4	6.8	1	1.7	2	3.4	7	11.9
25-26.....	10	13.5	3	4.1	5	6.8	2	2.7	0	0.0	7	9.5
27-30.....	5	7.5	2	3.0	2	3.0	1	1.5	0	0.0	3	4.5
31-35.....	1	5.0	0	0.0	0	0.0	1	5.0	0	0.0	1	5.0
36-40.....	1	15.6	1	15.6	0	0.0	0	0.0	0	0.0	0	0.0
Total....	209	11.0	22	1.2	103	5.4	53	2.8	31	1.6	187	9.8

* The percentage of the age group as a whole has been calculated by assuming that the findings in the 180 with hypertension who were not reexamined would correspond to the findings of the 209 reexamined and recorded in this table.

RECLASSIFICATION

On the basis of the results of the reexaminations, the students were divided into two main groups, primary hypertension and secondary hypertension. The primary hypertensions were further divided into transient hypertension, those with systolic pressures under 130 mm. on all but the first examination; intermittent hypertension, those with the majority of readings over 130 mm., and persistent hypertension, those with all readings 140 mm. or more. Table 3 shows the age distribution and the calculated percentage of students in each of these groups. This calculation of percentage is made on the assumption that the 180 students with systolic pressures of 140 mm. or more who were not reexamined would have shown the same occurrence of secondary transient, intermittent and persistent hypertension as the 209 who were reexamined. The series, of course, is too small to justify fully such an assumption, but it is made in order to get some idea as to the proportions of these various groups in the student body as a whole.

SECONDARY HYPERTENSION

Whenever the physical examination revealed any condition that might cause an increased blood pressure, the case was considered as one of secondary hypertension. In Table 4 these various conditions are shown.

Hyperthyroidism was diagnosed four times among this group. Heart lesions were considered as a cause of hypertension only when there was a defect of the aortic valve. These cases were easily recognized because of the accompanying low diastolic pressure. The diagnosis of nephritis was based on the persistent occurrence of albumin and casts in the urine, a decreased ability to secrete concentrated urine as shown by the Mosenthal test and, in some cases, an increase of the blood metabolites. It is, of course, possible that in some of these students the urinary findings

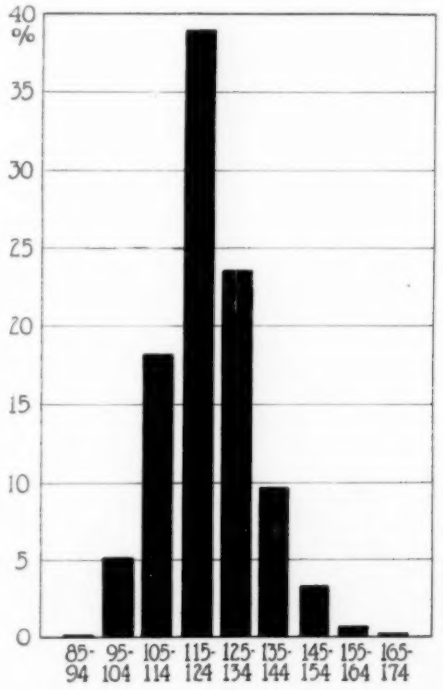

Fig. 9.—Percentage frequency of various pressure groups of 10 mm. for total 1923-1924 group.

were caused by an arteriosclerosis in the kidneys, the cases actually belonging in the group of primary hypertensions.

Ten students in the group reexamined showed albuminuria with no other evidences of nephritis. Eight of these had transient, one intermittent and one persistent hypertension. Since hypertension and this type of albuminuria may be evidences of the same general condition, these ten students were considered as having primary, rather than secondary hypertension. The calculated proportion of the 3,538 students who showed a secondary hypertension was —1.2 per cent.

PRIMARY HYPERTENSION

When no condition could be found which would account for an increased blood pressure, the case was considered as one of primary hypertension. A calculated total of 9.8 per cent. of the entire number examined in 1922 and 1923 showed such primary hypertension. The

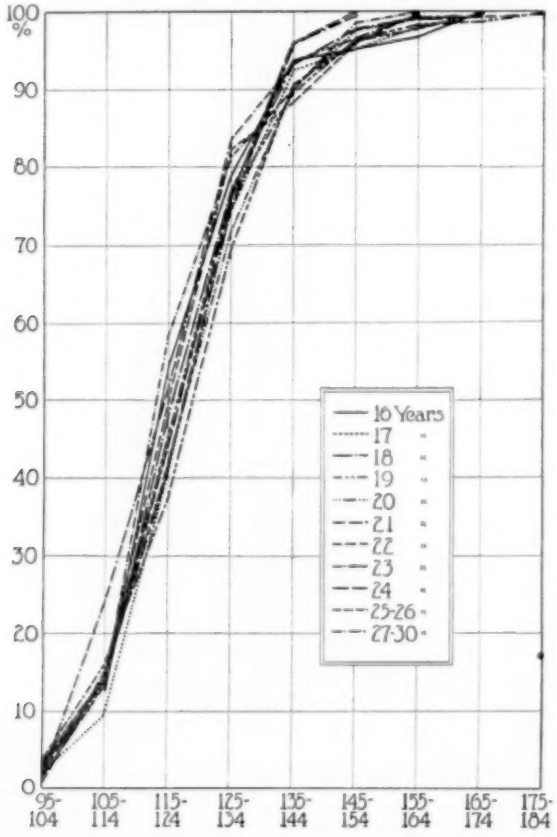

Fig. 10.—Percentage summation curves for each age group in 1922.

occurrence of this condition among the various age groups is surprisingly uniform, except for the 20 year old group, in which it is only 5.6 per cent. The groups of students above 25 years of age are too small for the percentages to be of much significance.

On reexamination the cases with primary hypertension were further subdivided into transient, intermittent and persistent hypertension.

TRANSIENT HYPERTENSION

When a student's systolic blood pressure was recorded on the first examination as 140 mm. or more but on subsequent examination was always found to be below 130 mm., his condition was considered as one of transient hypertension. In these students the increased blood pressure

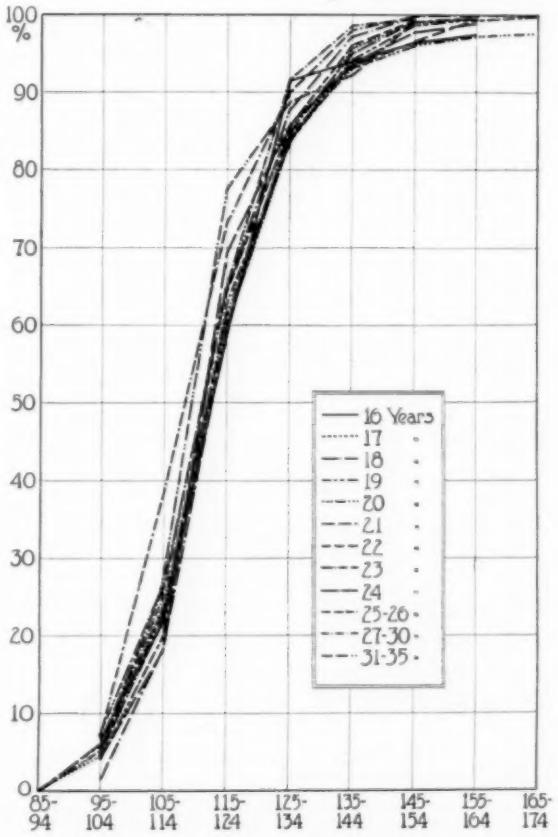

Fig. 11.—Percentage summation curves for each age group in 1923-1924.

probably was caused chiefly by the excitement and hurry of university registration; consequently, it probably has little if any significance. A calculated total of 5.4 per cent. of the entire class had transient hypertension. The distribution by age groups shows the condition most frequent in students of 16, 17, 24 and 25-26 years.

One would expect more excitement over entering college among students of 16 and 17 years than among students a few years older. It also may be surmised that students who enter college at the age of 24 years or more tend to comprise a group more emotionally unstable than would be found in a cross-section of the population of the same age group. Some of these older students may have been teaching school or doing other work for years in order to save sufficient money to go to college. To them this event, of course, would be accompanied by a considerable amount of exhiliration. Others, after leaving high school, may have been unsuccessful in business and so turn to college with the hope that their deficiencies may be overcome. The number of these older students, however, is too small to be significant. The low percentage of transient hypertension in the 20 year old group is striking but no explanation is apparent.

TABLE 4.—*Causes of Secondary Hypertensions*

	Transient Hypertension	Intermittent Hypertension	Persistent Hypertension	Total
Hyperthyroidism	0	0	4	4
Heart lesion	1	2	6	9
Chronic nephritis	0	4	4	8
Chorea	0	1	0	1
Total	1	7	14	22

INTERMITTENT HYPERTENSION

When the original blood pressure record was 140 mm. or more and the majority of subsequent readings over 130, the case was called one of intermittent hypertension. The calculated total in this group was 2.8 per cent. The distribution, according to the various age groups, is quite uniform. It is impossible to say what the significance of this condition is, but it seems that when a young person frequently has high blood pressure, he must be at least a prospect for permanent hypertension later in life.

PERSISTENT HYPERTENSION

When the blood pressure was 140 or more on every reading, the condition was called persistent hypertension. The calculated total of students who fell into this group was 1.6 per cent of the entire class. The occurrence of this condition in the different age groups is somewhat irregular, but the groups are too small to be significant. What the future holds in store for these young persons with persistent hypertension, one cannot say definitely, but the group is worthy of particular study from many standpoints, especially as to familial tendencies with relation to hypertension and as to the further course of these individuals in relation to their systolic hypertension and the development of hyperpiesis, essen-

tial hypertension and cardiovascular diseases. Fisher [10] of the Northwestern Mutual Life Insurance Company reports that the death rate among 743 persons between the ages of 16 and 29 who were rejected for life insurance because of systolic blood pressures of from 10 to 50 mm. or more over the average for the age was 195.9 per cent. of the expected rate; that is, the actual death rate was almost double the expected death rate. Among persons of higher ages, the ratio was still greater.

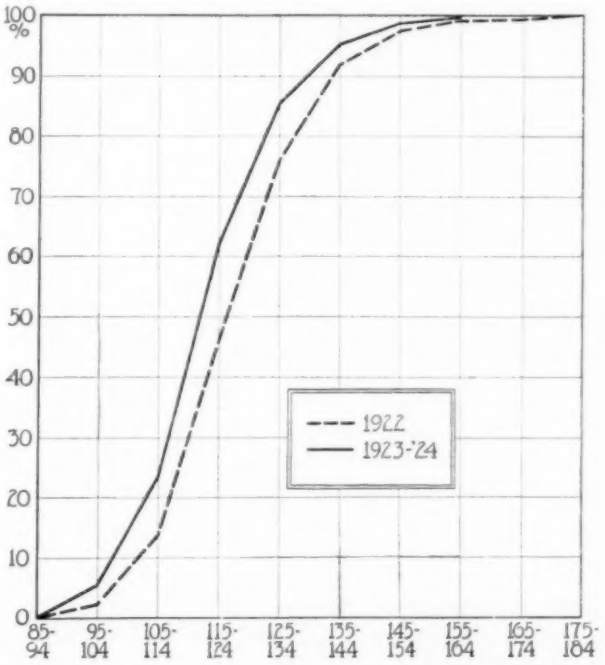

Fig. 12.—Percentage summation curves for entire 1922 and 1923-1924 groups.

WEIGHT AND HYPERTENSION

The tendency for hypertension to be most frequent in overweight people has been pointed out by life insurance companies and is now rather common information.[11] With this in mind, a preliminary study of the weights of the students who were reexamined for hypertension

10. Fisher, J. W.: Report of Blood Pressure Committee, Proc. A. Life Ins. M. Directors of America **9**:59, 1922-1923.

11. Hunter, Arthur: Weight and Blood Pressure, Proc. A. Life Ins. M. Directors of America **7**:199, 1920-1921.

was made. This did not include a thorough statistical analysis of the data. The results are given in Table 5. On this table no relationship between weight and transient or intermittent hypertension is apparent. In the small group that showed persistent hypertension, however, the most frequent percentage to occur, i. e., the mode, was 108 per cent. of normal; the average, i. e., the mean, was 106.6, and the median was 103. Only 3.4 per cent. were below 90 per cent. of normal weight, while 24.1 per cent. were over 110 per cent. of normal weight for age and height. This would suggest that even in young people there may be some relationship between weight and persistent hypertension.

TABLE 5.—*Weight of Students with Hypertension* *

Section	No. of Cases	Mode (Actual)	Mean	Median	Under 90 per Cent. of Normal Weight	Over 110 per Cent. of Normal Weight
A. Transient hypertension....	91	100	98.2	100	16.4%	12.0%
B. Intermittent hypertension.	51	92, 108	100.3	100	13.7%	17.6%
C. Persistent hypertension....	29	108	106.6	103	3.4%	24.1%
Total average.....	171	108	103.3	100	13.4%	15.8%

* The figures in the first four columns of this table represent the percentage that the weight is of normal. Calculations were made according to age and height with the use of the table of the Prudential Life Insurance Company.

VITAL CAPACITY AND HYPERTENSION

Table 6 displays the vital capacity readings, expressed in percentages of normal,[12] of the students in the various hypertension groups. In general the vital capacity seems high, but no relationship is evident between the type of hypertension and the percentage of vital capacity.

COMMENT

Although the etiology of hypertension is not yet understood, various contributory factors in its production, such as age, weight, etc., have from time to time been pointed out. Symonds,[13] in a statistical study of the blood pressures of 150,419 persons accepted for life insurance, found a difference of about 14 mm. between the systolic pressures of persons of light build and persons of heavy build, and about 11 mm. difference between the youngest and oldest age groups. Bell and Hartzell[14] emphasize the importance of body weight over age and show that the age increase in the average heart weight is due to increased body weight and the inclusion of cases of hyperpiesis. From this they inferred that

12. Myers, J. A.: Studies on the Respiratory Organs in Health and Disease, Am. Rev. Tuberc. **7**:161 (May) 1923.

13. Symonds, B.: The Blood Pressure of Healthy Men and Women, J. A. M. A. **80**:232 (Jan. 27) 1923.

14. Bell, E. T., and Hartzell, T. B.: Studies on Hypertension: The Relation of Age to the Size of the Heart, J. M. Res. **44**:473 (June) 1924.

the age increase in blood pressure is due to similar factors. Weitz [15] and others have observed the hereditary or familial character of hypertension. Alvarez [3] discusses the significance of such possible factors as sex, the war, the influenza epidemic, etc. And most physicians at one time or another have observed the great tendency of excitement and nervousness to increase blood pressure.

TABLE 6.—*Vital Capacity of Students with Hypertension*

Section	No. of Cases	Mode (Actual)	Mean	Median	Under 90 per Cent. of Normal	Over 110 per Cent. of Normal
A. Transient hypertension....	92	91	105.1	104	4.3%	27.1%
B. Intermittent hypertension.	51	89, 115	103.1	106	11.7%	39.2%
C. Persistent hypertension....	29	96, 103	100.0	103	17.2%	24.1%
Total average.....	172	96	103.7	104	8.7%	30.2%

On the basis of the studies reported in this paper, it would seem that there are several factors that may be etiologic in the production of high blood pressures in young persons. On the reexamination of 209 students, who on the entrance physical examinations showed systolic pressures of 140 mm. or more, 11 per cent. were found to have organic diseases, such as hyperthyroidism, aortic regurgitation, chronic nephritis, etc., to which the hypertension observed probably was secondary. Only 15 per cent. of the students with pressures of 140 mm. or more on first examinations showed persistent elevation of blood pressure. This is the group with real primary hypertension, the cause of which is, as yet, unknown. Twenty-five per cent. of the group had intermittent hypertension, a condition that many believe will develop in later life into a persistent hypertension. The other 49 per cent. had merely transient hypertension. These transitory increases of systolic blood pressure are responsible for about half the high blood pressures observed among university freshmen. It is probably true that certain individuals are more susceptible to rises of blood pressure than others, but the immediate cause in most cases is excitement or nervous tension. In our studies it was noted that blood pressures were lower when precautions were taken to eliminate excitement. Shepard and Diehl [16] pointed out that hypertension is more frequent among students from small communities than among those from larger cities. In studies on the need for mental hygiene among college students, Morrison and Diehl [17] observed that among students of a psychoneurotic nature the percentage

15. Weitz, W.: Zur Aetologie der genuinen odervasculären Hypertension, Ztschr. f. klin. Med. **96**:151 (Jan. 27) 1923.

16. Shepard, W. P., and Diehl, H. S.: Rural and Urban Health, J. A. M. A. **83**:1117 (Oct. 11) 1924.

17. Morrison, A. W., and Diehl, H. S.: Mental Hygiene Needs of Freshmen, J.A.M.A. **83**:1666 (Nov. 22) 1924.

of hypertension was twice as large as among the student body as a whole. The high incidence of hypertension noted by Alvarez among 16 and 17 year old students probably was due to the greater excitement that the younger boys and girls experience on entering college. But the greatest evidence of the influence of excitement is the fact that about

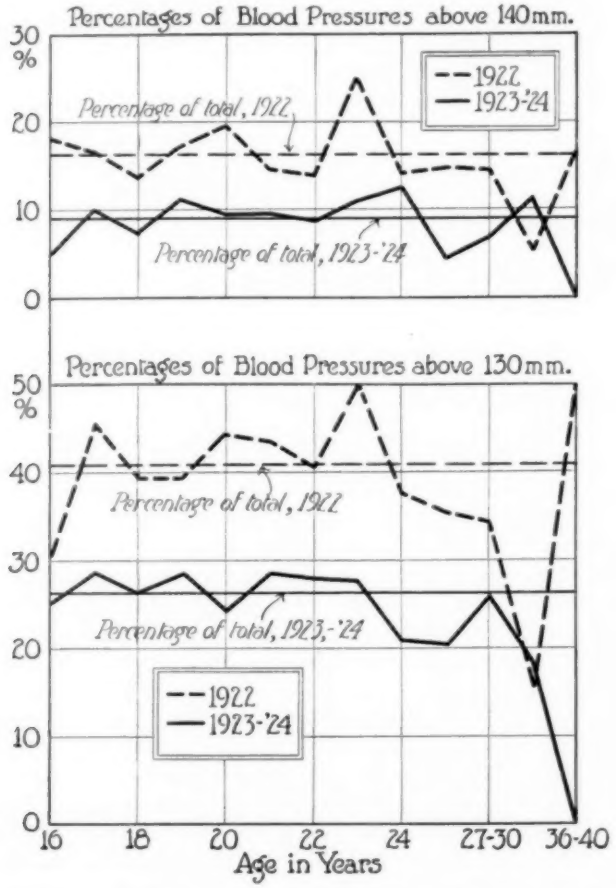

Fig. 13.—Percentages of blood pressures over 130 mm. and percentages over 140 mm. for each group in 1922 and in 1923-1924.

half the students who showed hypertension on the first examination were found to have normal blood pressures on reexamination.

The grouping of blood pressures around 120 mm., as evidenced by a mode of 120, a mean of 122.7, and a median of 122, offers no basis for a

suggestion that we should modify our ideas as to what constitutes normal blood pressures for young persons. Symonds [13] reported that the average (mean) systolic pressure for all builds at 20-24 years was 124.2 mm. Apparently, if the element of excitement can be eliminated, the generally accepted standards for blood pressure are adequate.

This group of apparently normal healthy young adults who already have shown persistent hypertension offers an unusual opportunity to observe the effect of hypertension on subsequent health and accomplishment. Every possible effort will be made to follow the group both in college and in later life.

CONCLUSIONS

1. A study has been made of the systolic pressures of the 5,122 young men who entered the University of Minnesota in the years 1922, 1923 and 1924.

2. Greater precautions to eliminate the influence of excitement were taken in 1923 and 1924 than in 1922, with the result that the blood pressures in these years were lower than in 1922.

3. In 1922, 16.2 per cent. had systolic pressures of 140 or more; in 1923 and 1924 only 9 per cent. showed this degree of hypertension. In the latter group, only 0.5 per cent. had systolic pressures of 160 mm. or more and 0.1 per cent. of 170 mm. or more.

4. Two hundred and nine students out of 389 who in the 1922 and 1923 entrance examinations showed systolic pressures of 140 mm. or more, were reexamined. Only 15 per cent. of these proved to have persistent hypertension.

5. The calculated proportion of the entire group examined who showed secondary hypertension was 1.2 per cent.; transient hypertension, 5.4 per cent.; intermittent hypertension 2.8 per cent., and persistent hypertension, 1.6 per cent.

6. Nervousness and excitement seem to be most important factors in the production of transient hypertension in young persons.

7. There seems to be some relationship in this group between overweight and persistent hypertension, but none between vital capacity and hypertension.

PATHOGENICITY OF TRICHOMONAS INTESTINALIS *

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The question of pathogenicity of *Trichomonas intestinalis* has long been debated without an apparent solution. The consensus of opinion among parasitologists at present seems to be in favor of nonpathogenicity of the flagellate. In fact, the majority of textbooks treat the infection as of minor importance. Barlow [1] states that the increase of trichomonas is the result and not the cause of the diarrhea. Manson and Bahr [2] refer to its presence as accidental and not due to a pathologic condition. Minchin [3] claims trichomonas to be entozoic in the human intestine and a harmless scavenger rather than a parasite. However, Rhamy and Metts [4] cite the incidence of local epidemic and endemic occurrence, and all the cases that came under their observation can be frequently traced to the same causes as acute and chronic diarrhea.

Lynch [5] emphasizes that it is a definitely pathogenic organism, and produces a mild enteritis manifested by intermittent diarrhea. Freund [6] believes that in some cases of enteritis characterized by diarrhea, abdominal distress and anemia *Trichomonas hominis* is a direct etiologic factor. A marked improvement or a complete recovery is obtained by its removal or a reduction in the number of the flagellates. Smithies [7] reports twenty-one cases of trichomoniasis, most of which are suggestive of a pathologic condition attributable to this infection, in his enterologic clinic. The catabolic products contained in a large number of these parasites may have a considerable influence as gastro-intestinal irritants, as one of the causes of metabolic changes in the digestive glands, and as a source of the clinical symptom complex of so-called autointoxication. Escomel,[8] strong in his belief of its definite pathology, considers its presence is liable to induce in the liver hepatic abscess similar to that caused by *Entameba dysenteriae*. The infection usually starts as chronic

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* From the Clinical Laboratories of the Battle Creek Sanitarium.

1. Barlow, N.: New Orleans M. & S. J. **69**:299 (Oct.) 1916.
2. Manson and Bahr: Tropical Diseases, Ed. 7, New York, William Wood & Co., p. 769.
3. Minchin: An Introduction to the Study of Protozoa, London, Edward Arnold, 1912.
4. Rhamy, B. W., and Metts, F. A.: Trichomonas, J. A. M. A. **66**:1190 (April 15) 1916.
5. Lynch, K. M.: Cultivation of Trichomonas and Question of Differentiation of Flagellates, J. A. M. A. **79**:1130 (Sept. 30) 1922.
6. Freund, H. A.: Arch. Int. Med. **1**:28 (Jan.) 1908.
7. Smithies, F.: Am. J. M. Sc. **156**:173 (Aug.) 1918.
8. Escomel: Lima, Sarmati y Ca., 1919, Bull. Soc. Path. exot., Paris **7**:657, 1914.

with intermittent acute attacks, and often induces ulceration, beginning at the rectum and decreasing in intensity upward. At necropsy, Boyd [9] found pseudomembraneous colitis extending from the ileocecal valve to the rectum. This seems to substantiate the findings made by Escomel.

Musgrave [10] brings out the fact that the pathogenicity of trichomonas in a diarrheal condition is generally accepted by experienced clinicians in the tropics, and credits it with being a cause of dysentery among children. He admits, however, that there can be only slight importance attached to it when present in small number in otherwise healthy persons, and that it is pathologic only when present in large numbers or associated with other parasites. Hudley [11] experimented with turkeys and found the flagellates in and beneath the mucosa and submucosa of the ceca, and concluded that they probably entered through the goblet cells in the glands of Lieberkühn, forced in by the peristaltic movement of the intestine in a similar manner to that in which trypanosomes enter the body. In reptile and batrachia, according to Plimmer,[12] trichomonas are often present in the circulation, and their presence is associated with a definite and recognizable lesion of the intestinal wall.

Haughwout [13] attributes its pathogenicity to the production of growth-inhibiting as well as toxic substances; to liberation of injurious metabolic products; to mechanical irritation of the mucous membrane when present in large number; to interference with absorption by adhering to the intestinal walls, and to destruction of the tissues. Levy,[14] in his findings in twenty subjects following saline purge, reports that all the cases can be traced to the history of diarrhea attacks at some time. Somewhat conservative views were expressed by Castellani [15] and Kofoid and Swezy,[16] who stated that diarrhea in these cases is often dependent on the number of trichomonas present. Kofoid and Swezy [17] further point out pentatrichomonas as a distinct species on account of its ability to engulf erythrocytes and digest them while the trichomonas does not, a point of view opposed to the nonpathogenic theory advanced by Wenyon and O'Connor.[18]

9. Boyd, M. F.: J. Parasitology **4**:168 (June) 1918; ibid. **5**:132 (March) 1919.

10. Musgrave, W. E.: Flagellate Infestations and Infections: Giardiasis, or Lambliasis; Trichomoniasis; Prowazekiasis, Cercomoniasis, Chilomastixiasis and Tetramitiasis, J. A. M. A. **79**:2219 (Dec. 30) 1922.

11. Hudley: J. M. Res. **36**:79, 1917.

12. Plimmer: Presidential Address, Royal Micros. Soc., London, 1912.

13. Haughwout, F. G.: Philippine J. Sc. **13**:217 (Sept.) 1918.

14. Levy, M. D.: Am. J. Trop. Med. **2**:1 (Jan.) 1922.

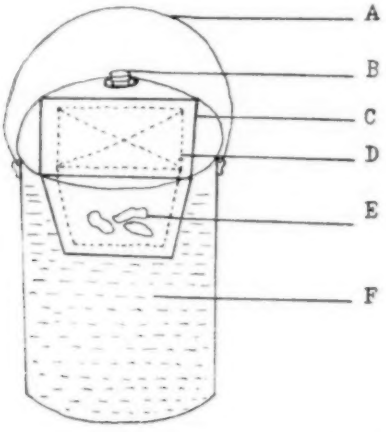
15. Castellani, A.: J. Trop. Med. **20**:198 (Sept. 1) 1917.

16. Kofoid, C. A., and Swezy, O.: Am. J. Trop. Med. **1**:41 (Jan.) 1921.

17. Kofoid, C. A., and Swezy, O.: Am. J. Trop. Med. **4**:33 (Jan.) 1924.

18. Wenyon and O'Connor: Human Intestinal Protozoa in the Near East, Welcome Bureau of Scientific Research, 1917.

During recent months (from July to October), I found considerable frequency in the occurrence of flagellates among the patients at Battle Creek Sanitarium, and this led me to investigate the question not only from the laboratory standpoint but also from a clinical one, hoping that a definite solution might be reached. The tropical zone is the natural climate for *Trichomonas hominis*. According to Barlow, the flagellate infection occurs in 25 per cent. of the cases treated; Lynch [19] reported 20 per cent. In this locality, however, 8 per cent. should be considered as probably the highest number obtainable, although some of our patients are from southern districts. Barlow,[20] however, states that most of the patients that came under his observation were from middle and eastern



Copper bucket; *A*, handle; *B*, stopper; *C*, cover; *D*, paper pail; *E*, feces, and *F*, hot water.

states. Using various laboratory findings and clinical data obtained from the department of internal medicine of the sanitarium, I shall endeavor to throw additional light on the subject.

The laboratory method for the detection of *Trichomonas hominis* need not be described fully here, as it has been presented by Hegner and Becker [21] and Lynch and Hogue.[22] The method employed in connection with this work was a modification of the one described by them, and is briefly given here.

19. Lynch, K. M.: South. M. J. **10**:286 (April) 1917.
20. Barlow, N.: Am. J. Trop. Med. **4**:23, 1924.
21. Hegner, L. W., and Becker, E. R.: Parasitology **9**:15 (Sept.) 1922.
22. Hogue, M. J.: Waskia Intestinalis, J. A. M. A. **77**:112 (July 9) 1921.

METHOD

Collection of Stool.—The stool used in the examination is not allowed to become cool at any time. It should be passed directly into a paper pail (2 quart [2 liter] oyster pail with a metallic clasp), and this pail placed immediately in a warm bucket, as shown in the accompanying illustration. The warm bucket must have been filled with water as hot as the hand can stand but not boiling. The specimen is sent at once to the laboratory for examination. Although Barlow advocates a fresh specimen that has not been subjected to external temperature, by using this method I often find positive cases when the findings are otherwise contrary.

Microscopic Examination.—A direct smear is made from the stool, preferably with a little fragment of mucus if present. A drop of physiologic sodium chlorid solution suffices to distribute the smear uniformly under a cover slip. The examination is made, on a warm stage especially provided for this purpose, first by low and then by high power to ascertain the morphology of the organism. It is necessary to examine several smears taken from different parts of the stool before a definite finding is reported. If the case is negative, a pea sized stool should be inoculated into the culture.

Culture.—The culture used for this purpose is the ovomucoid medium originated by Hogue. It is made as follows: The whites of six eggs should be beaten thoroughly with an egg beater, gradually mixed into 600 c.c. of boiling saline solution, and boiled for fifteen minutes. The mixture should be filtered by aid of a suction pump, first through a thin layer of gauze and then through cotton. The filtrate should be placed in 7 c.c. tubes, each of which should be autoclaved at 15 pounds (6.8 kg.) pressure for twenty minutes. A portion of about pea sized stool should be inoculated and incubated for twenty-four hours at 37 C. The flagellate, if present, is usually found on the surface of the medium, particularly against the sides of the tube. Several smears should be carefully scrutinized before a negative report is given. I found this method superior to the direct microscopic, especially in cases in which there was only slight suspicion of a positive finding. It is often the case that the culture method reveals the motility of flagellates when the direct method fails. The cyst formation of the flagellate is not included in the consideration, as several authors are agreed as to its absence. Although I do not agree with Lynch [23] entirely concerning the possibility of cyst formation, there is no doubt that the trichomonas undergoes a series of transitional stages in its morphology, i. e., from a round, cystlike structure to a fully organized, oval form with a characteristic jerky movement.

23. Lynch: New York M. J. **101**:886, 1915.

TABLE 1.—*Cases in Which Many*

			Fecal Analysis							Urinary Analysis						Metabolism	
Case	Age	Meat Consumption	Mucus	Blood	Gram-positive per Cent.	Gram-negative per Cent.	B. coli	B. welchii	B. acidophilus	Albumin	Casts	Sugar	Indican	Indol-Acetic Acid	Toxin Test	Carbon Dioxid Tension	Acetone
1	51	Moderate	0	0	35	65	++	+	+	0	0	0	16	+	+	42	0
2	48	Heavy	0	0	20	80	+++	+	0	0	0	0	4	+	+	37	+
3	62	Moderate	0	0	20	80	+++	+	0	0	0-1 Hyaline	0	0	+	Trace	36	+
4	64	Heavy	0	0	20	80	+++	+	0	0	0-2 Hyaline	16.80	0	Trace	+	36	Trace
5	27	Little	0	0	35	65	++	+	+	0	0	0	Trace	+	++	38	0
6	44	None	0	0	40	60	−	+	+	2½	3-4 Hyaline	0	Trace	Trace	Trace	28	+
7	55	None	0	0	20	80	+++	+	0	0	0-1 Hyaline	0	12	+++	++	36	0
8	58	Moderate	0	0	20	80	+++	+	0	0	0	0	0	+	Trace	42	0
9	37	Moderate	0	0	20	80	+++	+	0	0	0	0	0	+	Trace	39	Trace
10	32	Little	0	0	35	65	++	+	+	0	0	0	0	0	Trace	44	Trace
11	59	Little	0	0	20	80	+++	+	0	0	1-2 Hyaline	0	0	+	Trace	33	0
12	34	Moderate	0	0	15	85	+++	++	0	....	....	..	..	..	..	36	0
13	41	Little	0	0	15	85	+++	++	0	0	0	0	2	+	++	39	0
14	68	Heavy	Much	0	25	75	+++	+	+	0	0-1 Hyaline	0	0	0	0	37	+
15	45	None	Mixed	0	20	80	+++	+	0	0	0	0	Trace	0	Trace	42	Trace
16	26	Moderate	0	0	20	80	+++	+	0	0	0	0	0	0	0	40	0
17	41	Heavy	0	0	25	75	+++	+	+	0	0	0	2	+	Trace	41	0
18	48	Little	0	0	25	75	+++	+	+	0	0	0	5	Trace	Trace	37	0
19	57	Moderate	Some	0	20	80	+++	+	0	0	0	0	3	Trace	+	36	0
20	56	Little	0	0	20	80	+++	+	0	0	0	0	1	+	+	40	0
Positive, per cent....			15	0	..	..	100	100	35	5.2+	31.5+	5.2+	57.8+	78.9+	89.4+	..	40
Average.....			...	..	23.5	76.5	....	....	....	...	...	..	..	..	..	37.96	..

* In this and Table 2, C.V.R. means cardiovascular renal.

Blood Analysis			Gastro-Intestinal			Circulatory Symptoms: Blood Pressure					
Hemoglobin	Red Cells	White Cells	Symptoms	Proctoscopic Exam.	Nervous Symptoms	Systolic	Diastolic	Cardiac	Nutritional Symptoms	Additional Laboratory Tests	Diagnosis
90	4,700,000	10,200	Pain; flatulence; nausea; constipation	Spastic colitis	Headache; irritability; insomnia	114	76	0	None	.....	Neurocirculatory asthenia; intestinal toxemia
90	4,400,000	7,200	Pain; flatulence; constipation	Spastic colitis	Irritability	112	70	0	None	.....	Intestinal toxemia
88	4,450,000	5,700	Pain; flatulence; constipation	Spastic colitis	Headache; irritability; insomnia	134	82	0	Loss of weight	Gastric, 0, 0, 0, 0, 0, 0	Obesity; intestinal stasis
84	4,420,000	4,500	Pain; flatulence; nausea; vomiting; constipation	Rectal stasis	Headache; irritability	100	64	0	Rundown; loss of weight	.....	Diabetes mellitus
90	4,800,000	5,700	Flatulence; nausea; constipation	Colonic and rectal stasis	Headache; irritability	106	60	0	Rundown; loss of weight	.....	Neuropathic
87	4,620,000	7,500	Pain; flatulence; constipation	Rectal stasis	None	175	115	C.V.R.*	Rundown; fever; loss of weight	.....	Cardiovascular renal disease
90	4,850,000	6,000	Constipation	Spastic colitis	None	220	170	C.V.R.	Rundown; loss of weight	.....	Cardiovascular renal disease; cholelithiasis
90	4,580,000	5,700	Flatulence; constipation	Colonic stasis	Irritability	106	68	0	None	.....	Intestinal toxemia
90	4,740,000	5,400	Flatulence; constipation	Spastic colitis	None	110	60	0	None	.....	Intestinal toxemia
88	4,950,000	6,300	Pain; flatulence; nausea; constipation	Spastic colitis	Headache; irritability	118	58	0	Rundown; loss of weight	Gastric, 36, 14, 30, 66, 60, 78	Gastric neurosis
87	4,880,000	5,400	Flatulence; constipation	Rectal stasis	None	192	92	C.V.R.	Rundown; loss of weight	.....	Chronic interstitial nephritis; hemiplegia
87	4,710,000	9,300	Pain; flatulence; constipation	Rectal stasis	Headache; irritability	98	60	0	None	Eosinophils, 1 per cent.	Migraine
90	4,870,000	6,600	Pain; flatulence; constipation	Spastic colitis	None	112	72	0	Rundown	.....	Intestinal toxemia
88	4,830,000	6,300	Flatulence; constipation	Colonic stasis	Headache; irritability; insomnia	160	90	0	Rundown; loss of weight	.....	Mucous colitis
87	4,310,000	6,900	Flatulence; constipation	Rectal stasis	None	82	58	..	Rundown	.....	Mucous colitis; obesity
87	4,740,000	8,100	Flatulence; constipation	Spastic colitis	Headache; irritability	108	62	0	Rundown; loss of weight	.....	Constipation (spastic); retroversion of uterus
87	4,900,000	6,000	Flatulence; constipation	Spastic colitis	Headache; irritability	116	88	0	Rundown	.....	Ostearthritis; colitis
87	5,020,000	7,200	Flatulence; nausea; vomiting; diarrhea	Mucous colitis	Headache; irritability; insomnia	114	72	..	Rundown	Gastric, 0, 0, 0, 0, 0, 0; eosinophils, 2.5 per cent.	Hypothyroidism; hysteria; diarrhea
87	4,700,000	5,700	Pain; flatulence; nausea; constipation	Spastic colitis	Headache; irritability	146	84	0	Rundown	.....	Constipation (spastic)
85	4,720,000	4,500	Pain; flatulence; constipation	Spastic colitis	Headache; irritability; insomnia	110	70	0	Rundown	Gastric, 18, 0, 14, 18, 34, 0	Cholelithiasis; constipation (spastic)
..	.....	.....	Pain..... 50 Flatulence.....96 Nausea.....30 Vomiting..... 5 Constipation..96 Diarrhea..... 5		Headache..60 Irritability 70 Insomnia..25	...	..	..	Rundown.70 Fever..... 5 Loss of weight...45		
86.8	4,621,500	6,510									

Fixation of Wet Smear.—When a positive finding is made, the smear is fixed and stained in order to determine the number of flagellates, which differentiate it from *Pentatrichomonas hominis*, present in the species. Hot Schaudinn's solution followed by Heidenhain's iron-hemotoxylin is used in the staining.

Morphology of Trichomonas Hominis.—This is carefully studied by following the description given by Kofoid and Swezy. Especial attention is directed toward a clear differentiation of the species from *Pentatrichomonas hominis*. For full details on the morphology of the flagellate, the reader may refer to the article by Kofoid and Swezy.

The pathogenicity of *Trichomonas hominis* is centered on gastro-intestinal symptoms, particularly diarrhea of varying degrees. In order to make the study conclusive, not only the laboratory findings in feces, urine and blood, as well as the metabolism, but also the symptom complex of gastro-intestinal, cardiac, nervous and nutritional origins have been tabulated. The entire group of the cases has been divided into two classes, one having a large number of *Trichomonas hominis* in an average microscopic field, and the other a few in each. This enables the reader to make a comparative study of the cases as to the severity and complication in the clinical entities. Further, in several instances gastric analysis and differential blood count are added, thus making the clinical and laboratory pictures more comprehensive.

Laboratory findings tabulated here are by no means complete. Only those data necessary for interpretation of the subject have been selected.

FECAL ANALYSIS

Fecal examination is of prime importance in dealing with flagellate infection. It has been proved by experiments carefully conducted by Hegner [24] that the putrefactive type of bacterial flora is unfavorable for the growth of intestinal flagellates, while the aciduric type is favorable for their proliferation. His contention on this unique finding is indeed very interesting. Metabolic products of aciduric bacteria provide a medium suitable for *Trichomonas muris*, while indol, skatol and other amino-acid derivatives are injurious to the growth and activities of the flagellates. Thus, with albino rats, he found *Trichomonas muris* the most abundant after the flora had become fermentative by prolonged feeding of the animals with dextrin and a mixed diet. I cannot say at this moment that his experimental deduction is fully in accord with that of Hegner, the full report of which will be published at a later date.

As shown in the accompanying tables, the fecal examination reveals several items in regard to the presence of blood and mucus, the per-

24. Hegner, R. W.: Am. J. Hygiene **3**:180 (March) 1923.

centage of gram-positive and gram-negative bacteria, and the relative proportion of *Bacillus acidophilus*, *Bacillus welchii* and *Bacillus coli*-like organisms, expressed by the plus sign.

Mucus and blood are seldom found in the cases in which a large number of *Trichomonas hominis* are detected in the stools. The finding is contrary to what Woodcock,[25] Lynch, Escomel and Rhamy have brought out. I agree with Levy in making a statement so conservative as "a few instances." Smithies found blood in sixteen cases out of twenty-one, but in none of twenty cases (Table 1) that came under our observation was blood evident either chemically or macroscopically. It tends to prove that *Trichomonas hominis*, differing from *Entameba dysenteriae*, is not a hemolytic protozoa; neither has its presence any relation with inflammatory changes brought about in the intestinal wall, if any are present. Diarrhea, so characteristic of the infection, as well as the blood and mucus findings, as indicated by many authors, provide the basis in some part of the present study.

The terminology of "normal stool" as defined by Smithies in his article is not clear to me. However, throughout all our cases there has not been a single stool which could be called "normal" in a bacteriologic sense. The findings, therefore, correlate with those of Smithies and, incidentally, are quite contrary to what Hegner advocated in his experimental study. *B. acidophilus* exhibits neither symbiosis nor antagonism in connection with the presence of *Trichomonas hominis* in the stools. Whatever may be the metabolic products of *B. acidophilus* and of putrefactive bacteria, no appreciable effect is noted on the proliferation of the flagellates. Throughout all the cases, the predominance of coli-like organisms cannot be disputed. Coupled with this, *B. welchii* is present in all, thus proving that indol, skatol and hydrogen sulphid are little hindrance to the growth and multiplication of *Trichomonas hominis*. It is safely stated, therefore, that the type of intestinal flora is independent of the flagellate. Regardless of the flagellates, the flora depends exclusively on the condition of nutrition and the kind of diet given. The putrefactive flora harbors *Trichomonas hominis* as frequently as the fermentative type. The change of flora from aciduric to putrefactive does not exhibit any advantage in decrease of the number of *Trichomonas hominis*, and the determination of the infection can never be induced by feeding the patients a diet favorable for the proliferation of putrefactive bacteria. Such an assumption requires no comment on the therapeutics of the disease.

Contrary to Hegner's belief, the transformation has taken place, though slowly, as *Trichomonas hominis* disappeared from the stools.

25. Woodcock: J. Roy. Army M. Corps. **29**:290, 1917.

The carbohydrate diet exaggerates the peristalsis of the intestine in such a way as to expel its content very rapidly; thus, the absorptive power of the intestine, particularly of the ascending and transverse portions, becomes more or less retarded, and this affords a chance for the flagellates while actively motile to escape into the stools. In the condition of putrefactive flora, however, the toxic products are quickly absorbed by intestinal mucus, and the feces are formed or of scybalic consistency—the result of complete absorption. During the absorptive process of the intestine, a large number of *Trichomonas hominis* lose their morphologic characteristics; some even undergo structural changes, and doubtless partial or complete dissolution of protoplasm may be brought about. In my experiment with albino rats, at levels further away from the ileocecal valves, the number of *Trichomonas muris* became noticeably diminished. Thus, in the cecum the average number of *Trichomonas muris* in the rats fed with stock diet was eighty-two; at the hepatic flexure, five, while in the descending colon it was three, and in the feces, one. This can be explained by the greater absorptive power of the ascending and the transverse colons and the fact that the cecum fails to function. In the putrefactive condition, the sojourn of the flagellates in the cecum is explained by the favorable alkalinity and also by the lessened onward migration of fecal matter from the cecum to the lower part of the colon.

URINARY ANALYSIS

Urinary examination is not considered as important as fecal, since the infection is primarily of intestinal origin. Only the few data necessary for the interpretation of the flora are tabulated, together with the albumin, sugar and types of casts. Indican, indol, acetic acid and toxin tests serve the purpose in dealing with the bi-products of putrefaction. In looking over the table, irregularity of findings is noted despite the presence of a large number of *Trichomonas hominis* in the stools. The possible relationship of the flagellates to putrefactive bi-products, as mentioned by Hegner, is quite doubtful in view of our clinical observations.

METABOLISM

The metabolism of the subjects showed no appreciable variation in the study. None of the patients presented abnormality in carbon dioxid tension, with the exception of one or two. In these this was attributed to the organic diseases from which the patients were primarily suffering; the flagellate infection had no bearing on the condition. These carbon dioxid tension findings correlate with those made by Barrow. The presence of acetone in expired air in a few instances does not bear out the pathogenicity of flagellate infection.

BLOOD ANALYSIS

Next to the fecal examination, the blood analysis gives an index no less important in the clinical study of trichomoniasis. In most parasitologic diseases, the secondary anemia and eosinophilia are common occurrences. Musgrave and Smithies attribute the low hemoglobin and low red blood count in the infection to the pathogenic effect of *Trichomonas hominis*, while Barrow asserts that the blood picture remains constant, if there are no other diseases present that could account for the abnormality in the hematologic picture. Throughout there was no case in which hemoglobin was higher than 90 per cent. in the first series, and 91 per cent. in the second, while the lowest were 67 and 63 per cent., respectively. The number of erythrocytes presented a practically normal picture, with the two exceptions in which the lowest hemoglobin was quoted. If it is granted that the comparatively low hemoglobin with normal red cell count is of flagellate origin, the clinical picture thus shown is nothing but the result of the average findings obtainable in such a series of cases, and cannot be attributed solely to the trichomonas infection. One of the exceptional cases cited above was diagnosed as pernicious anemia. Out of ten cases of trichomoniasis, Freund found two associated with pernicious anemia. The white cell count showed a wide variation, from 5,400 to 10,200. Leukopenia was more prevalent in the whole series than leukocytosis. Although Barrow asserts that leukopenia occurs in any protozoan disease, it cannot be interpreted as a consequence of the trichomonas infection, as these patients came here primarily for treatment for some other chronic disorder of nervous, cardiac or nutritional origin. In such, leukopenia may occur.

DIFFERENTIAL BLOOD COUNT

A differential blood count was made on five cases in which marked eosinophilia was absent. The highest eosinophil count obtainable was 2.5 per cent. and the lowest 1 per cent. The test was added in case the blood picture was suggestive of anemia, either primary or secondary. In each instance, there were some irregularities in the morphology of the erythrocytes. From this finding coupled with the blood count and hemoglobin determinations, the cases were diagnosed. Rhamy and Metts report a moderate degree of eosinophilia, from 6 to 12 per cent., in all the cases, while Smithies quotes sixteen cases of eosinophilia out of twenty-one. Barrow states that there were no cases of trichomonas infection that showed a single eosinophil in several examinations of blood stains. Eosinophilia is considered as one of the clinical indexes to most of the parasitic infections, but with trichomoniasis it has no particular bearing.

GASTRIC ANALYSIS

A fractional gastric test also was made in eight cases in which there were three cases of hypochlorhydria, one case of hyperchlorhydria, two cases of achylia and two cases of normal acidity. The tables given here tend to show that hypochlorhydria is more frequently found with trichomoniasis than otherwise. Marked hypochlorhydria was observed by Levy, and eleven cases of achylia and eight cases of hypochlorhydria

TABLE 2.—*Cases in Which Fea Trichon*

			Fecal Analysis							Urinary Analysis						Metabolism		Blood
Case	Age	Meat Consumption	Mucus	Blood	Gram+ per Cent.	Gram− per Cent.	B. coli	B. welchii	B. acidophilus	Albumin	Casts	Sugar	Indican	Indol-Acetic Acid	Toxin Test	Carbon Dioxid Tension	Acetone	Hemoglobin
21	40	Little	0	0	20	80	+++	+	0	0	0	0	0	+	+	36	Trace	85
22	80	Little	Some	Trace	20	80	+++	+	0	0	0	0	4	0	+	36	0	88
23	49	Heavy	0	0	25	75	+++	+	+	0	0	0	0	+	Trace	36	0	88
24	75	Moderate	0	0	25	75	+++	+	+	0	0	0	7	0	+	39	Trace	87
25	60	Heavy	0	0	40	60	+	+	+	0	0	0	0	+	+	39	Trace	90
26	22	Heavy	0	0	20	80	+++	+	0	1½	0	0	16	+	+	39	0	91
27	62	Moderate	0	0	30	70	++	+	+	Trace	3-4 Hyaline	0	3	+	Trace	36	0	86
28	51	Moderate	0	0	40	60	+	+	+	0	0	24.32	0	+	0	38	Trace	88
29	58	Heavy	0	0	20	80	+++	+	0	0	2-3 Hyaline	0	Trace	+	+	38	Trace	90
30	65	Moderate	Little	++	20	80	+++	+	0	0	0	0	3	+	++	30	0	92
Positive, per cent....			30	30	..	..	100	100	50	20	20	10	60	80	90	..	50	..
Average.....			..	..	24	76	....	....	....	..	..	..	..	..	..	35.8	..	90.2

by Smithies. Although our series do not bear out the high abnormal findings of Smithies, there is a tendency toward the predominance of hypochlorhydria, if any. The findings, however, are not conclusive, as such a condition may be attributable to metabolic and nutritional disturbances, from which the majority of our patients suffer and which are, in my opinion, an accidental coincidence in the course of trichomoniasis.

The clinical symptoms tabulated here are the sum total of the present complaints of the patients abstracted from case histories, together with the necessary data obtained through physical examinations by their attending physicians. For the sake of convenience, I classify the symptoms under four headings: gastro-intestinal, nervous, circulatory and nutritional disturbances, the first being the most important and the rest more or less subsidiary to the first.

Trichomona Hominis Were Found

Blood Analysis			Gastro-Intestinal		Nervous	Circulatory Symptoms			Nutritional	Additional Laboratory	Diagnosis
						Blood Pressure					
Hemoglobin	Red Cells	White Cells	Symptoms	Proctoscopic Exam.	Symptoms	Systolic	Diastolic	Cardiac	Symptoms	Tests	
91	5,000,000	5,100	Flatulence	Rectal stasis	None	95	65	..	None	Gastric, 0, 0, 0, 28, 42, 18	Arthritis; chronic follicular prostatitis
88	4,770,000	6,000	Pain; flatulence; nausea; constipation	Spastic anus	None	130	75	..	Rundown; loss of weight	.....	Arteriosclerosis
90	4,750,000	9,200	Flatulence; constipation	Colonic stasis	Headache	200	110	C.V.R.	None	.....	Obesity; cardiovascular renal disease
87	4,900,000	6,000	None	.....	Irritability	120	70	Chronic myocarditis	None	.....	Rheumatoid arthritis
90	4,800,000	5,200	Pain; flatulence; constipation	Colonic stasis	Irritability; insomnia	160	90	0	Rundown	Gastric, 0, 0, 8, 12, 10, 14	Hypochlorhydria; intestinal toxemia
93	4,550,000	7,500	Pain; flatulence; constipation	Colonic stasis	Headache; irritability; insomnia	130	60	0	Rundown	Gastric, 0, 10, 0, 20, 10, 22	Neurosthenia
86	4,230,000	9,000	Pain; flatulence; diarrhea	.....	Headache; irritability; insomnia	90	50	Tachycardia	Rundown; loss of weight	Gastric, 0, 0, 0, 0, 0; eosinophils, 1 per cent.	Diarrhea
88	4,900,000	5,500	Pain	.....	None	170	84	Myocardial insufficiency	None	Eosinophils, 1.5 per cent.	Diabetes mellitus; obesity
90	4,940,000	5,100	Flatulence; nausea; constipation	Rectal stasis	None	100	60	0	Rundown; loss of weight	.....	Hemorrhoids; urticaria
63	2,600,000	3,200	Flatulence; nausea; vomiting; constipation	Rectal stasis	Irritability	95	50	Mitral regurgitation	Rundown; loss of weight	Eosinophils, 2 per cent.	Pernicious anemia
..	.....	.....	Pain.....50 Flatulence.....80 Nausea.....30 Vomiting.....10 Constipation..50 Diarrhea.....10		Headache..30 Irritability 40 Insomnia..30	...	..	..	Rundown.60 Loss of weight...40		
86.2	4,559,000	6,810									

GASTRO-INTESTINAL SYMPTOMS

Pain.—This pain may be either epigastric or colonic. The epigastric pain may be interpreted as of mechanical, chemical and nervous origin, and the colonic as due either to local or functional disturbances. Local pain and tenderness that is not accompanied by a constitutional manifestation has little diagnostic value. Out of twenty cases in Table 1, ten had this symptom; in Table 2, five. In these series, the pain symp-

tom occurred in one-half the cases, seven of which were epigastric in nature. In the majority of the cases, the abdominal pain was distributed in the right iliac fossa, which is suggestive of cecal disorders.

Flatulence.—This was a very common occurrence in our cases, especially in those with intestinal putrefaction. The symptom was prevalent in 90 per cent. of the first series and in 80 per cent. of the second. The flatulence may have a vague significance, but depends largely on the associated disorders, chiefly of gastro-intestinal origin.

Nausea and Vomiting.—Nausea was shown in six cases of the first series and in two of the second, and there were only two patients in the whole series who vomited. Nausea and vomiting in these series were brought about by pernicious anemia, diabetes and nervous reflex due to irritation of vagus and phrenic nerves or perhaps to organic diseases of the central nervous system, and are by no means symptoms referable only to trichomoniasis.

Constipation and Diarrhea.—The pathogenicity of trichomoniasis has been based chiefly on the production of diarrhea, either acute, chronic or intermittent. This has been emphatically brought out by Woodcock, Rhamy, Freund, Smithies, Lynch, Barrow and Escomel. In their clinical symptomatology, without diarrhea there is nothing to indicate that *Trichomonas hominis* plays a pathogenic rôle. A remarkable contradiction was shown in our series, in which there were only two cases of diarrhea out of thirty cases of trichomoniasis, while constipation occurred in nineteen cases of the first series and in six of the second, and the remainder had neither constipation nor diarrhea in their clinical histories. Moreover, constipation was an outstanding feature in trichomoniasis in our experience. It can be safely stated, therefore, that diarrhea, if present, is due to some other factor of mechanical, chemical or nervous origin. I agree with O'Connor and Wenyon that diarrhea is a more or less accidental happening in the course of a disease due to some other causes. While trichomonas may be associated with a diarrheal condition, it cannot be considered as a cause of diarrhea; this has been clearly proved in our daily examination of stools in which *Trichomonas hominis* is seldom encountered in watery specimens. Some of these cases of diarrhea have been attributed to the excessive fermentative activity of intestinal bacteria, while the consideration of *Giardia* (*Lamblia hominis*) and *Entameba dysenteriae* in this connection also may deserve special mention.

PROCTOSCOPIC EXAMINATION

Proctoscopic examination shows that the majority of the cases of trichomoniasis have been diagnosed as spastic colitis or stasis at some

point in the colon. These findings are further suggestive of constipation, commonly prevalent among the patients.

NERVOUS SYMPTOMS

Nervous symptoms, such as headache, irritability and insomnia, cannot very well be considered as resulting from the trichomonas infection, and are either the result of some other pathologic condition or of a neuropathic tendency revealed in the history. These are tabulated merely to present some data necessary for comparison with the studies made by other authors. It is evident that the symptoms mentioned in the foregoing are more referable to intestinal autointoxication than to any other single factor.

NUTRITIONAL SYMPTOMS

General debility, such as loss of weight, a general run down condition and fever are not attributable to the trichomoniasis alone. Any disease related to disturbances in nutrition or of a systemic nature, so common among our patients, manifests similar results.

Nervous and nutritional symptoms, therefore, are not to be considered as conclusive evidence of trichomoniasis, but instead are the common symptoms of many chronic ailments. According to other writers, the important symptom, so far as diagnostic value is concerned, is diarrhea, a cardinal symptom of trichomoniasis. If the positive theory holds true, therefore, the patients should experience a certain degree of diarrhea, either acute, chronic or perhaps intermittent, with constipation, accompanied by a characteristic clinical syndrome. Conclusively, however, constipation is a uniform finding in our series. Nervous and nutritional symptoms are nothing but the outcome of constipation and are not due to trichomoniasis, in which they have no significance.

CIRCULATORY SYMPTOMS

The blood pressures shown in the table are not out of the ordinary, considering the age of the patients and the diagnosis given. Hypertension in our series is mostly suggestive of cardiovascular complication, while hypotension indicates nutritional disturbance of some sort.

The amount of meat consumed by the patients before entering the institution was tabulated in order to show the possible effect of high protein on the number of *Trichomonas hominis*. That a high meat diet is productive of intestinal proteolysis needs no special mention. According to Hegner, bi-products of putrefaction, such as indol, skatol, hydrogen sulphid and ammonia, are unfavorable to the existence of *Trichomonas muris* in the large intestine. The higher the extent of putrefaction, the fewer the number of *Trichomonas muris* in the

intestine. If his theory can be applied clinically, the low protein consumers are more liable to harbor *Trichomonas hominis* than the high meat eaters. Tables 1 and 2, however, does not encourage the hypothesis. Irrespective of the diet taken, the flagellates were present in large number.

The diagnoses of the cases are tabulated to show the symptom complex exhibited by the patients correlated with the organic or functional disorders rather than with trichomoniasis.

Comparative study of trichomoniasis in relation to the number of the flagellates is also made in order to ascertain the possible variation as to its pathogenicity. Musgrave and Levy are inclined to believe that the number of *Trichomonas hominis* is directly proportional to the extent of the infection. In the average findings tabulated, there is not enough evidence in either series to be conclusive in this regard.

CONCLUSION

1. *Trichomonas hominis* is not a pathogenic but a harmless flagellate present in the large intestine.

2. Whether they are present in large or small number, neither laboratory nor clinical pictures bear evidence conclusive enough to warrant pathologic diagnosis.

3. Diarrhea, mentioned by many as characteristic of trichomoniasis, has no clinical aspect in these series; instead constipation is a common occurrence with no diarrheal history in the past. Furthermore, proctoscopic diagnosis emphasizes the fact that constipation is a usual accompaniment in these cases.

4. Nervous symptoms and nutritional disturbances as manifested by these cases are attributable not to the presence of *Trichomonas hominis*, but to some organic or functional disorder or to constipation secondary to such.

5. The intestinal flora is independent of the presence of *Trichomonas hominis*. The type of intestinal flora does not alter the number of the flagellates. Hegner's assumption in regard to albino rats is not feasible in its clinical application.

PRIMARY VASCULAR NEPHRITIS, OR RENAL PERIARTERITIS NODOSA *

J. JAY KEEGAN, M.D.
OMAHA

A recent case at the University Hospital afforded an unusual opportunity by early nephrectomy and later by necropsy to observe the development of a primary vascular nephritis of infectious origin. The operative specimen presented the characteristic pathologic appearance of periarteritis acuta nodosa and the necropsy specimen, two months later, showed the transformation of this lesion into early arteriosclerosis and chronic vascular nephritis. Associated with this renal vascular pathologic condition was a similar lesion of the cystic artery of the gallbladder, the pancreatic artery and the splenic artery.

REPORT OF CASE

History.—Mrs. C., aged 24, entered the University Hospital, Sept. 13, 1924, with the complaint of general malaise of three weeks' duration, weakness and loss of weight, from 118 to 82 pounds (53.5 to 37.2 kg.), over a period of several months. The history was unreliable as the patient was a morphin addict; she had been using "bromidia" for several weeks and was irrational. She was moaning but not complaining of pain. She looked older than her age and had a grayish pallor. Physical examination revealed marked dental infection. The heart, lungs, abdomen, pelvis and extremities were negative. The temperature was 103, pulse 120, respirations 25. The leukocyte count totaled 20,000, polymorphonuclears 90 per cent. The specific gravity of the urine was 1.020; albumin and sugar tests were negative; there were no casts or red blood cells; a culture of a catheterized specimen on blood agar was negative. A blood culture was negative; the blood sugar was 139 mg.; the spinal fluid was normal; blood and spinal Wassermann reactions were negative. The mental condition improved in a few days; the elevation of temperature and polymorphonuclear leukocytosis persisted, but the patient made no complaint and insisted that she felt fine. Roentgenograms of her teeth showed many alveolar abscesses. Distinct tenderness and rigidity were elicited in the right side of the abdomen and in the right kidney region.

Surgical consultation was called, September 26, on account of the persistence of the abdominal symptoms in the right side. There were sepsis and a few pus cells in the urine but no other localizing signs. An exploratory operation was advised, with a preoperative diagnosis of a surgical condition of the right kidney. At operation, September 29, a small anterior right abdominal incision was made and the gallbladder, stomach, appendix and pelvis were explored with negative findings. This incision was closed and the right kidney explored through a right flank incision. The kidney seemed slightly enlarged, the fatty capsule being rather adherent; it was removed. Gross section of this kidney showed numerous white miliary nodules all located at the corticomedullary border. These looked like miliary tubercles (Fig. 1). Two or three larger white areas with hemorrhagic borders were found in the cortex. The cortex otherwise was rather pale, but with normal markings, averaging 6 mm. in thickness. The capsule stripped easily leaving a smooth surface, except for the few larger slightly elevated nodules noted above.

* From the University of Nebraska College of Medicine.

Fig. 1.—Cut surface of right kidney removed at operation, showing whit miliary nodules and hemorrhagic infarct due to swollen and infiltrated arcuat arteries (actual size).

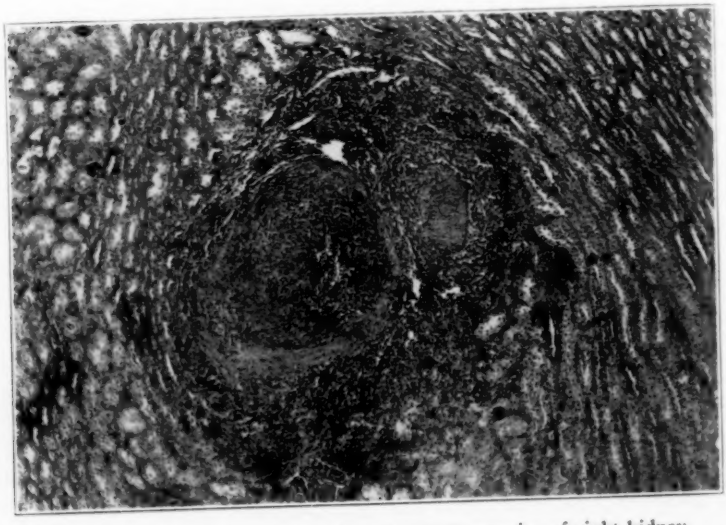


Fig. 2.—Acute inflammatory lesion of arcuate arteries of right kidney.

Microscopic examination of sections of this kidney showed the miliary nodules to be markedly swollen and infiltrated arcuate arteries (Fig. 2). The inflammatory reaction involved the entire artery wall, intima, media and adventitia. The intima was markedly swollen from edema and infiltrated with numerous mononuclear cells and polymorphonuclear leukocytes. In places there was extensive necrosis of this swollen intima. A small lumen containing a few red blood cells usually persisted. The muscularis in many places was almost indistinguishable on account of the inflammatory cell infiltration; elsewhere it was fairly well defined but with swollen cells. The adventitia was densely infiltrated and markedly thickened with mononuclear cells, a few polymorphonuclear leukocytes, an occasional eosinophil and edema. The process was definitely limited to the artery wall; it did not extend appreciably into the surrounding kidney tissue. Search for bacteria in kidney sections stained by the Giemsa method

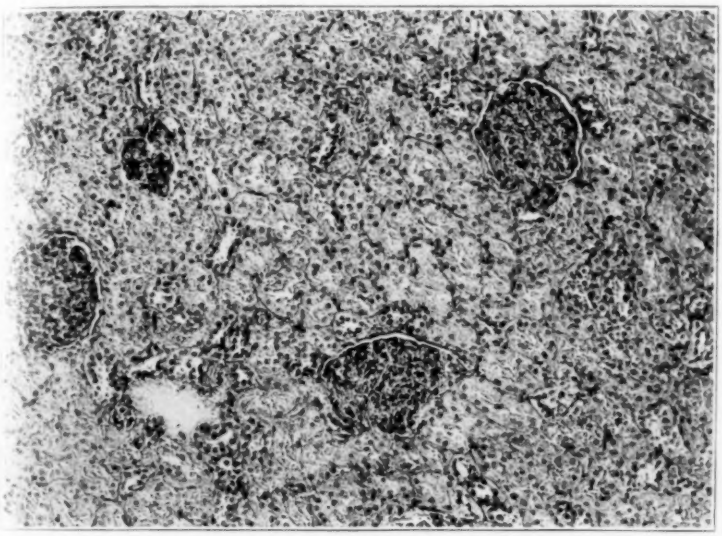


Fig. 3.—Cortex of right kidney.

was negative. Section of one of the larger necrotic and hemorrhagic areas in the cortex showed it to be a typical infarct with complete anemic necrosis in the center and hemorrhage at the border. The tributary artery was found thrombosed. The vascular lesion appeared limited to the arcuate arteries; it was rarely found extending into an interlobular artery or involving the larger vessels entering the hilum of the kidney. The glomeruli throughout the cortex, except in the infarcted areas, were practically normal in appearance (Fig. 3). There was no infiltration, swelling nor rupture of the loops. Most of them appeared rather bloodless, while a few were congested. The convoluted tubules were swollen and granular with some vacuolation, indicating marked granular degeneration. The nuclei stained clearly. The lumina of the tubules were almost absent, making identification under low power difficult. The interstitial tissue showed no infiltration and no congestion. Occasionally an area of granular material was found, which was interpreted as edema. A diagnosis of acute and subacute obliterating arteritis limited to the arcuate arteries was made. It was interpreted as being infectious in origin, blood borne and in all probability bilateral.

The patient made a stormy postoperative partial recovery, the temperature gradually dropping to 99-100, the pulse to 100-110. Blood chemistry, October 9, showed a nonprotein nitrogen of 43 mg. and creatinin of 2 mg. The patient was allowed to be up and was discharged, October 19, feeling fairly well.

The patient reentered the hospital November 6, on a stretcher, very nervous, apparently in severe pain and quite tender in the right lumbar region. She said that her kidneys had been very active during the preceding week, with nocturia six times, unassociated with pain. She had been feeling fairly well till three days prior to reentrance, when she first noticed shortness of breath and some pain in the back and sides. These symptoms increased rapidly and forced her to bed. Her temperature on entrance was 102, pulse 130, respirations 30; the leukocyte count was 40,000; polymorphonuclears were 82 per cent., red blood cells 4,200,000, hemoglobin 60 per cent. The urine had a specific gravity of 1.018, albumin 2 plus, numerous white blood cells, a few red blood cells and many granular casts. The blood nonprotein nitrogen was 43 mg., creatinin 1.5 mg. The systolic blood pressure was 125, diastolic 90. The pulse was rapid and irregular, temperature around 101 and respirations 25 for the next few days. The output of urine was markedly diminished. With increased elimination, the acute symptoms subsided except that the patient was very weak and still complained of pain and tenderness in the right side of the abdomen and the right lumbar region. The urinary findings cleared considerably, the specific gravity dropping to 1.011, the albumin to 1 plus; there were a few white blood cells and granular casts. A Mosenthal specific gravity test day, November 17, showed fixation at 1.008 with retention, as follows:

	11 a. m.	1 p. m.	3 p. m.	5 p. m.	7 p. m.	7 a. m.
Specific gravity.....	1.008	1.008	1.008	1.008	1.008	1.007
Amount	75 c.c.	90 c.c.	105 c.c.	90 c.c.	100 c.c.	550 c.c.

The total twenty-four hour intake was 1,650 c.c.; output, 910 c.c. There was slight puffiness of the eyelids, but no general edema. The phenolsulphonephthalein output was less than 5 per cent. in two hours. A blood culture was negative. The Mosenthal test day was repeated November 20 with practically the same result:

	11 a. m.	1 p. m.	3 p. m.	5 p. m.	7 p. m.	7 a. m.
Specific gravity.....	1.008	1.008	1.008	1.008	1.008	1.008
Amount	90 c.c.	90 c.c.	110 c.c.	90 c.c.	100 c.c.	540 c.c.

The total twenty-four hour intake was 1,600 c.c.; output, 920 c.c. The patient left the hospital November 23, against advice, as the prognosis was considered very poor.

The patient was returned to the hospital November 25, on a stretcher, with marked dyspnea and orthopnea, some edema of the feet and slight puffiness of the eyelids. The temperature was 99, pulse 108, respirations 50. There was no heart murmur. The pulse was very weak, the systolic pressure was 100, diastolic 70. Mucous râles were heard in the bronchi. The leukocyte count was 29,600; polymorphonuclears were 84 per cent.; red blood cells totaled 3,500,000, and hemoglobin 60 per cent. The urine had a specific gravity of 1.005, albumin 2 plus (14 mg. per hundred cubic centimeters) and microscopically showed pus cells 1 plus, a few red blood cells and fairly numerous granular casts. The phenolsulphonephthalein output was less than 5 per cent. in two hours. The patient appeared very nervous, although she dozed at short intervals. She vomited considerable mucus and a little blood. There was slight improvement under digitalis therapy, although the pulse remained irregular and rapid—120, and dyspnea and orthopnea persisted. The temperature was subnormal. She complained of pain in her chest, November 27, and a pericardial friction rub was heard. November 28, a systolic murmur was heard over the mitral area. On this day her fluid intake was 2,460 c.c. and the urine output 990 c.c. She became rather drowsy; the lungs filled up with fluid and death occurred November 30, at 3:50 p. m. Necropsy was performed at 8 p. m.

Necropsy.—The body was that of . white, fairly well developed but emaciated woman. The skin was pale, except for many small bluish pigmented areas over both

pectoral, upper arm and anterior thigh regions. There was slight edema of the ankles and surgical scars in the right rectus and the right lumbar regions.

The wall of the abdomen was thin; the peritoneum was smooth and glistening; there was no free fluid. There were adhesions to the under side of the right rectus scar, also a separate firm fibrous adhesion laterally between the gallbladder and the anterior abdominal wall. The liver was 8 cm. below the costal margin in the midclavicular line, mottled yellow and dark red. Microscopic section of the liver showed a marked congestion about the central veins and corresponding granular degeneration of the liver cords. The portal areas were nearly normal. There was no arterial pathologic change in the sections examined. The gallbladder was of normal size and adhered by fibrous bands to the adjacent pylorus, colon and omentum. The fundus was mottled dark red with punctate hemorrhages and a general intense vascular injection. The wall was thickened and somewhat resistant. The aspirated bile was thin, pale and contained yellow flakes. Cultures of this bile on blood agar were negative.

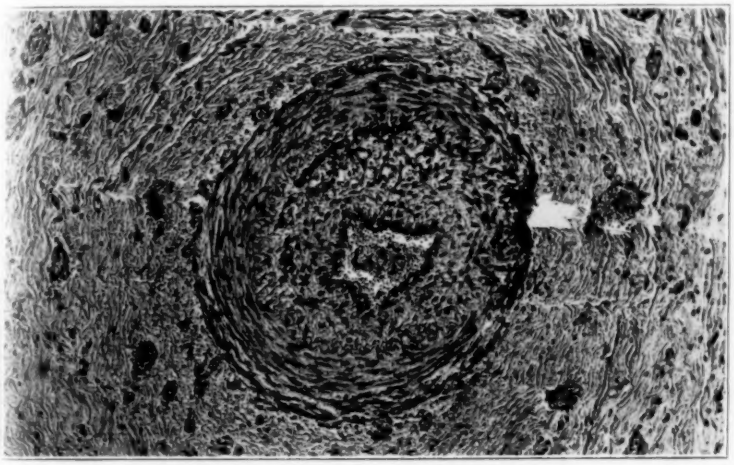


Fig. 4.—Cystic artery of gallbladder, showing greatly thickened intima.

When the gallbladder was opened, the wall measured 3 mm. in thickness; the mucosa was pale and elevated into soft, rounded, bulbous-like folds and projections. This appeared due to a loose swelling of the submucosa. Smears from the fixed submucosa showed an occasional gram-positive diplococcus but no pus cells. Dissection at the neck of the gallbladder showed an even greater thickening and congestion of the wall. Dissection of the hepatic artery and its branches disclosed the cystic branch of darker color, thickened walls and narrowed lumen. This pathologic condition began abruptly at the origin of the cystic artery and did not involve any portion of the right or left hepatic arteries, which were dissected a considerable distance into the liver tissue.

Microscopic sections of the neck of the gallbladder showed the cystic artery with an extreme thickening of the intima about twice the width of the remaining wall (Fig. 4). This thickening was due to a proliferation of fibroblasts and the deposit of an abundant loose fibrillary matrix. The nuclei were mostly round or oval and lenticular, taking a basic stain. The fibrillae also took a basic stain to a considerable degree, in comparison with the collagen fibrils of mature connective tissue. A rare polymorphonuclear leukocyte was found. The lumen

of the artery was a small channel lined by rounded endothelial cells and containing red blood cells. The internal elastic lamina was intact and normal appearing except at one side, where both it and the muscularis were not distinguishable. In this region there was a greater density of fibroblastic cellular tissue with a few inflammatory cells. The muscularis elsewhere was entirely normal. The adventitia likewise was negative for inflammatory cell infiltration but fused imperceptibly with a rather dense white fibrous tissue of the gallbladder wall. In this wall no smooth muscle fibers could be distinguished. There were numerous dilated thin walled blood vessels, evidently veins and capillaries. The mucosa of this region showed a few normal glands but little surface epithelium. The submucosa was moderately infiltrated with mononuclear

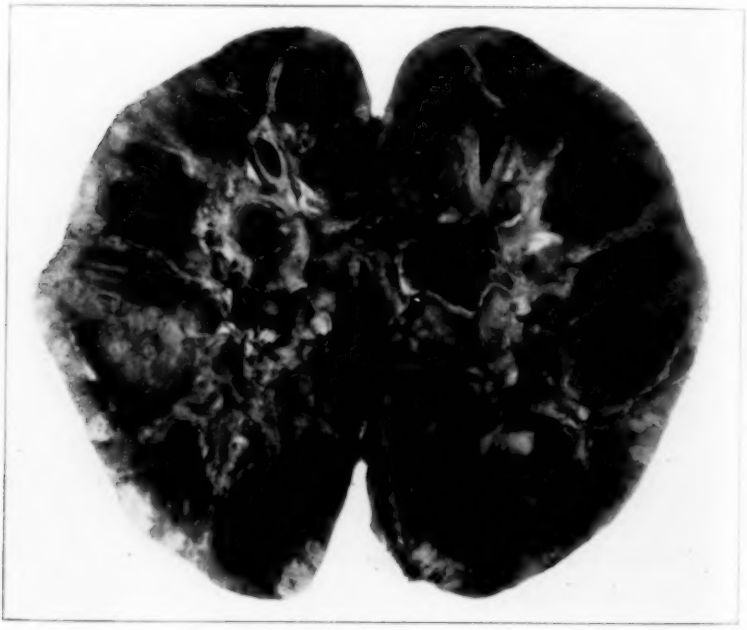


Fig. 5.—Cut surface of left kidney removed at necropsy, showing white infarcts, thickened arteries and narrowed cortex (actual size).

cells. There was almost no infiltration in the gallbladder wall proper. Microscopic sections through the fundus of the gallbladder showed practically the same pathologic condition.

The stomach and small and large intestines showed no gross pathologic change. The pancreas was pale and lobulated. Microscopically, there were very definite arterial lesions in the pancreas, consisting of a marked thickening of the intima by fibroblastic proliferation, variable destruction of the media by fibrosis and slight inflammatory cell infiltration and a marked increase of fibrous tissue in the adventitia. The acinous tissue showed considerable irregular granular degeneration, possibly postmortem. The islands varied likewise from normal to marked degeneration. The spleen was slightly enlarged, dark red, firm and contained a small hemorrhagic infarct. Microscopic sections showed one artery with marked intimal thickening and fibrosis of the wall similar to

that just described in the gallbladder and pancreas. Another artery in the same section showed no pathologic condition. The arterioles of the splenic corpuscles adjacent to the thickened artery showed marked hyaline degeneration and swelling of the entire wall. Others were normal. The infarcted area was of characteristic degenerated appearance. One bordering splenic arteriole had a marked fibrous thickening of the entire wall. A large artery in another section taken beyond the apex of the infarct showed an obliterating intimal fibrous thickening with an organized thrombus in one branch.

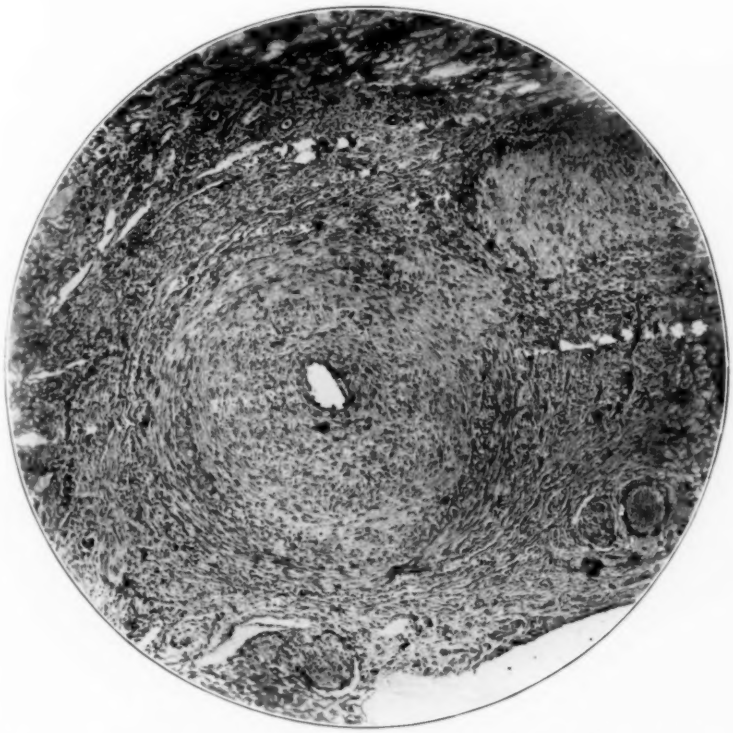


Fig. 6.—Renal interlobar artery, showing extreme fibrous thickening of intima.

The right kidney was absent, its bed filled with fibrous tissue with no evidence of infection. The left kidney was slightly decreased in size, weighing 225 gm., was somewhat adherent in its bed and was mottled with dark red and lighter areas. The capsule stripped easily, leaving an irregular mottled surface. Several yellowish white elevated areas proved by section to be anemic infarcts varying in size from a few millimeters to a centimeter in diameter. The intervening cortex was generally depressed and reddish. The cut surface (Fig. 5) showed a distinct thinning of the cortex, the average width being 4 mm., contrasted with a width of 6 mm. in the right kidney, removed at operation two months earlier. Also, the line of differentiation between cortex and medulla was somewhat indistinct compared to the right kidney. The larger arteries were dissected in the hilum of the kidney. There was no

pathologic condition of the larger subdivisions, but the lumen could not be followed into the interlobar branches. The walls there appeared thickened, firm and white.

Cross section of one of these arteries showed a pin point red lumen and thick fibrous walls. Microscopically, this artery possessed an enormously thickened fibroblastic intima which measured fully six times the thickness of the muscularis (Fig. 6). The very small lumen was lined with a single layer of normal endothelium. There was no inflammatory cell infiltration in the thickened intima. The internal elastic lamina was very distinct. The muscularis was of normal appearance. The adventitia was slightly increased and infiltrated.

Fig. 7.—Renal arcuate artery, showing almost complete fibrosis of wall, extremely thickened intima, an organized and canalized thrombus, and moderate perivascular mononuclear cell infiltration.

Microscopic sections of the kidney tissue proper showed the same process of fibroblastic intimal thickening in the arcuate arteries, extending occasionally into the interlobular arteries. In the arcuate arteries there was a greater involvement of the muscularis, which was not distinguishable in places owing to fibrosis and inflammatory cell infiltration. The adventitia also was more involved, thicker and considerably infiltrated. The lumen of some arteries contained organized and canalized thrombi (Fig. 7). The extension into interlobular arteries was chiefly as a fibroblastic intimal thickening, although the adventitia

showed some corresponding thickening. This process was irregular, in places involving only one side of a vessel, the other being normal (Fig. 8). At no place did it extend into the vas afferens or glomerular loops.

Connective tissue stain (picro-fuchsin) of these pathologic arteries showed the thickened intima taking the characteristic fuchsin of collagen fibrils, although not as intensely as mature white connective tissue. The glomeruli in most regions appeared normal except for congestion. The tubules showed a marked atrophy (Fig. 9). The cells of the convoluted tubules were flattened and bounded dilated lumina. The interstitial spaces were widened so that there appeared to be an increase of tissue. Connective tissue stain showed a moderate increase of loose collagen fibrillae. There was very little inflammatory cell infiltration. Irregular areas throughout the kidney showed the effects of more complete vascular obliteration. Where the process was gradual, the glomeruli showed hyaline degeneration or fibrosis, and the surrounding tubules showed complete atrophy and disappearance (Fig. 19). Their place was taken by a loose connective tissue moderately

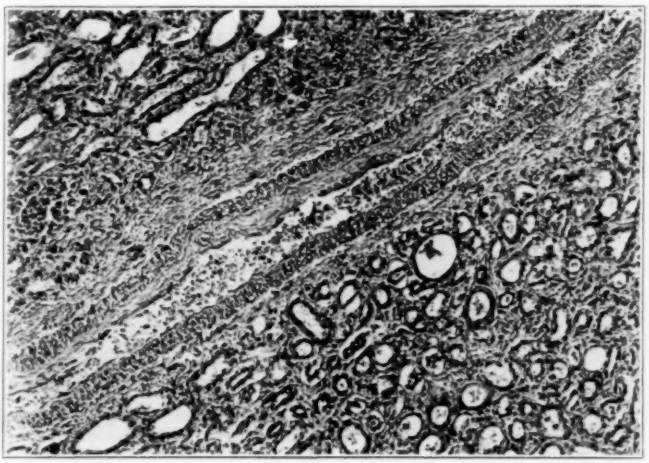


Fig. 8.—Renal interlobular artery, showing unilateral fibrous intimal thickening and corresponding increase of adventitia.

infiltrated with mononuclear cells. When the vascular obliteration was more sudden from thrombosis, characteristic complete necrosis of anemic infarcts appeared with beginning organization at the periphery.

Both pleural cavities contained a considerable amount of slightly cloudy straw colored fluid. The serous surfaces were smooth except for adhesions to the mediastium. The lungs were soft and crepitant throughout. The cut surface exuded frothy fluid. Microscopically, the alveolar septums were slightly thickened and congested. There was no infiltration. The bronchioles were negative. The pericardial cavity contained about an ounce (30 c.c.) of slightly cloudy fluid. The serous surfaces were covered with a thin, white fibrinous layer. The heart appeared slightly enlarged; the wall of the left ventricle measured from 1.5 to 2 cm. in thickness and was firmly contracted. The valves were entirely negative for vegetations or sclerosis. The coronary arteries were dissected and showed no pathologic change. Microscopic sections of the myocardium showed large well preserved cells. There was no thickening of the arteries or perivascular infiltration.

COMMENT

Acute localized inflammation of the smaller arteries of various organs of the body has been described in numerous reports under the name of "periarteritis nodosa." The first clear description of the microscopic pathology of this condition and the application of the name are credited to Kussmaul and Maier [1] in 1866, although the first gross description was given by Rokitansky [2] in 1852. Recent excellent reviews of the literature of the subject are given by Lamb,[3] 1914, and

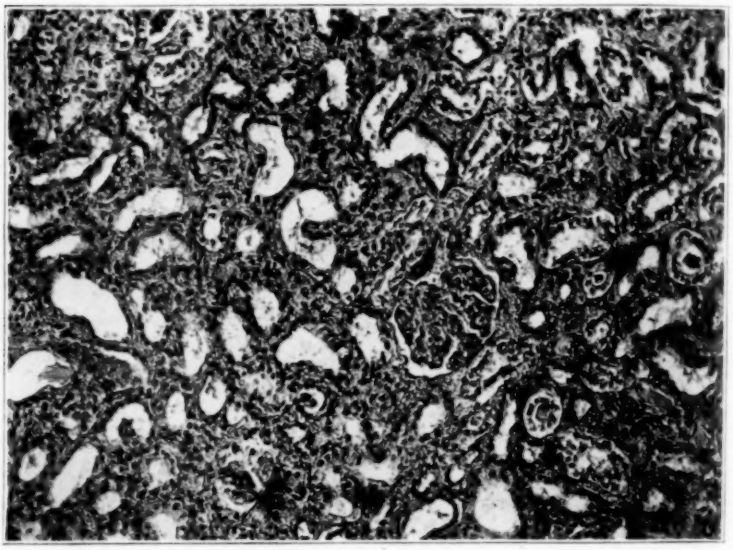


Fig. 9.—Cortex of left kidney, showing marked tubular atrophy and increase of interstitial tissue.

Ophüls,[4] 1923. Over seventy cases have been recorded, chiefly in the European literature. The disease probably is as common in this country but goes unrecognized on account of the difficulty of clinical diagnosis

1. Kussmaul and Maier: Eine bisher nicht beschriebene eigenthumliche Arterienkrankung die mit Morbus Brightii und rapid fortschreitender allgemeiner Muskellahmung einhergeht, Deutsch. Arch. f. klin. Med. **1**:484, 1866.

2. Rokitansky: Aneurysmenbildung sammtlicher Arterien mit Ausnahme die Aorta, und der meisten ansehnlichen primitive Aste derselben, ferner mit Ausnahme der Gehirnarterien, Denkschr. d. k. Akad. d. Wissensch, Vienna, **4**:49, 1852.

3. Lamb, A. R.: Periarteritis Nodosa: A Clinical and Pathological Review of the Disease, Arch. Int. Med. **14**:481 (Oct.) 1914.

4. Ophüls, W.: Periarteritis Acuta Nodosa, Arch. Int. Med. **32**:870 (Dec.) 1923.

and unfamiliarity with its pathology. It has been said to be almost 100 per cent. fatal because in all recorded cases the patients have died, but the idea has been expressed by many that both its record of rarity and its high mortality are probably due to the fact that antemortem diagnosis is not made and consequently only fatal cases are recorded.

The clinical picture is that of an acute or gradual onset of obscure sepsis with emaciation, weakness, prostration, fast pulse, marked leukocytosis and frequently intermittent pain in the abdomen. The pathologic findings are well marked nodules in the wall of the smaller arteries with frequent small aneurysms or thrombotic obstruction and infarc-

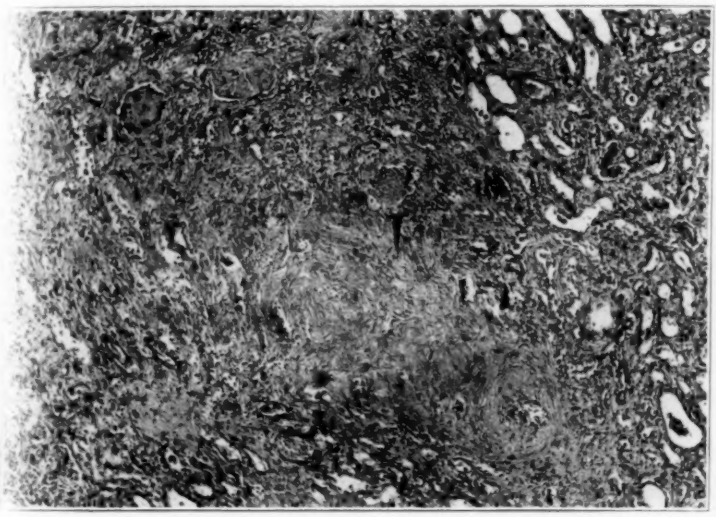


Fig. 10.—Cortex of left kidney, showing extensive hyaline degeneration and fibrosis from gradual arterial obliteration.

tion. The coronary arteries of the heart and the smaller arteries of the kidneys are oftenest involved, although the brain and other organs or tissues may be similarly involved. Usually the organs affected are multiple, although the process was found in only one organ in a number of reports. Fishberg [5] reports a case of six days' duration in which lesions were limited to the kidneys. Other writers call attention to the extension of the arterial inflammation of the kidneys directly into the interstitial tissue causing an interstitial nephritis,[4] or extension into the glomeruli causing an acute or subacute glomerulonephritis.[3] Changes in the composition of the urine are usually present and in some cases

5. Fishberg, A. M.: Zur Kenntniss der Periarteritis nodosa, inbesondere der Histiopathogenese, Virchows Arch. f. path. Anat. **240**:483, 1923.

death has occurred from uremia. The microscopic pathologic condition is an inflammatory cell infiltration usually involving all elements of the artery but characteristically most marked and occasionally alone in the adventitia or perivascular tissue. There has been much discussion as to the site of the primary pathologic condition in the artery wall. The etiology is unknown but a considerable amount of evidence suggests a relationship to streptococcus infection, particularly of the rheumatic group. The rather consistently negative blood, urine and tissue cultures, and the inability to find micro-organisms in tissue sections, as in this case, has prevented general acceptance of streptococcus etiology.

The pathologic condition found in the right kidney in this case, coupled with the preceding obscure septic history of a few weeks' duration, leaves little room for doubt that this was primarily a case of periarteritis acuta nodosa similar to many others reported. The most significant observations, however, were those which developed subsequent to the right nephrectomy. Nocturia and frequency appeared within a month or about two months from the onset of symptoms, and were quickly followed by symptoms of cardiac decompensation. The low kidney phenolsulphonephthalein output, low fixation of specific gravity, slight increase in blood nonprotein nitrogen, albumin, casts and cells in the urine all gave further evidence of a failing kidney function from vascular insufficiency. Death occurred in characteristic manner for primary vascular nephritis, by cardiac decompensation, retention of fluids, late uremic symptoms, subnormal temperature, fibrinous pericarditis and pulmonary edema.

The pathologic condition of the left kidney removed at necropsy, more than three months from the onset of illness and two months from the right nephrectomy, showed a characteristic early stage of chronic primary vascular nephritis. The acute lesions of the arteries of the right kidney were found transformed in the left kidney into early arteriosclerosis. The most prominent feature of these arteries was the great thickening of the intima by young white fibrous tissue. This markedly constricted the lumen and led to anemia of the kidney cortex with atrophy, fibrosis and infarction. The cortex was narrowed, the tubules markedly atrophied and a replacement interstitial fibrosis was under way in varying degree. The symptoms of chronic vascular nephritis presented by this case might be interpreted in sequence from the pathology as follows: Acute vascular infection and infarction in the kidneys led to little urinary change; subsequent gradual fibrotic intimal obliteration of the arteries led to tubular atrophy, with probable loss of reabsorptive power and consequent nocturia and low fixed specific gravity. The rapidity and severity of the arterial obliteration led to cardiac decompensation with less blood flow through the arteries

and glomeruli and resultant decreased urine output, nitrogen retention and terminal uremia.

The kidney pathology of this case suggests that a considerable number of cases of chronic vascular nephritis may have their origin in a mild attack of renal periarteritis nodosa. The kidneys are cited by Lamb [3] as being most frequently involved in the reported cases, although Ophüls [4] placed the coronary arteries of the heart first and the kidney arteries second.

The term "chronic vascular nephritis" is not clearly defined in the minds of many. Ordinarily it has been applied to the senile arteriosclerotic red granular kidney with little functional disturbance. In recent years, added significance has been placed on primary vascular lesions of the kidneys by the work of Jores,[6] Löhlein,[7] Gaskell,[8] Volhard and Fahr.[9] The first to call attention to the prominence of sclerosed arteries in microscopic sections of chronic nephritis were Johnson [10] and Gull and Sutton.[11] Johnson accurately observed the thickened intima of the primary contracted kidney but interpreted it as a greatly hypertrophied internal longitudinal muscular layer. Gull and Sutton [11] gave the first interpretation of the primary contracted kidney as due to vascular change. They insisted that the contraction was primarily due to the alterations in the small arteries of the kidney. They held that the main thickening was in the adventitia, that it was diffuse and spread into the surrounding tissues. They named the process arterio-capillary fibrosis.

Jores [6] revived the views of Gull and Sutton, asserting that the small artery change was a true arteriosclerotic process and part of a general small artery change affecting many organs, particularly the brain. He first described the fat in the wall of these sclerotic arterioles as a characteristic feature. Löhlein [7] likewise pointed out the enormous thickening of the smallest vessels of the kidney with fat change as the main diagnostic point of primary contracted kidney. Gaskell [8] studied the same subject with similar conclusions. He subdivided the vascular group of kidney disease into two divisions; the first was the senile

6. Jores, L.: Ueber die Arteriosklerose der Kleinen Organarterien und ihre Beziehungen zur Nephritis, Virchows Arch. f. path. Anat. **178**:367, 1904.

7. Löhlein, M.: Ueber Nephritis nach dem heutigen Stand der pathologish-anatomischen Forschung, Ergebn. d. inn. Med. u. Kinderh. **5**:411, 1910.

8. Gaskell, J. R.: On the Changes in Glomeruli and Arteries in Inflammatory and Arteriosclerotic Kidney Disease, J. Path. & Bacteriol. **16**:287, 1912.

9. Volhard, F., and Fahr, T.: Die Brightsche Nierenkrankheit, Berlin, 1914.

10. Johnson, G.: A Case of Chronic Bright's Disease with Rapidly Fatal Sanguineous Apoplexy, Brit. M. J. **1**:256, 1872.

11. Gull, W., and Sutton, H. G.: On the Pathology of the Morbid State Commonly Called Chronic Bright's Disease with Contracted Kidney (Arterio-capillary Fibrosis), Brit. M. J. **1**:620, 1872.

arteriosclerotic kidney due to extension of sclerosis of the aorta and larger vessels into the arterial branches of the kidney, causing disuse atrophy and degeneration of groups of glomeruli and their tubules by obliteration of interlobular arteries. There were no clinical symptoms of kidney disease and the blood pressure was seldom elevated or the heart enlarged. The second division was the "genuine Schrumpfniere," or "primary contracted kidney," which was due to primary arteriosclerosis of the small arteries. This was a part only of a general pathologic complex consisting of hypertrophic changes in the heart and aorta and vascular changes in the kidney and other organs, in particular the brain. It occurred much earlier in life than the senile arteriosclerotic form, usually in patients between 34 and 50 years of age. The conspicuous and important change was the extreme thickening with fat change of the smallest arteries of the kidney, the arteriae afferentes especially, but also of the interlobular arteries.

Volhard and Fahr [9] made a somewhat similar division of arteriosclerotic kidney changes into (*a*) the pure arteriosclerotic forms and (*b*) the combination form, "genuine Schrumpfniere," or primary contracted kidney. In the pure arteriosclerotic group, they included all forms with vascular change that did not enter the glomeruli. They called attention to the well known fact that while sclerosis of the larger and middle sized renal arteries might be a conspicuous feature of the renal histology and might cause puckering and scarring of the renal surface, such sclerosis was not correlated with any typical clinical picture. On the other hand, whenever there was present any considerable thickening of the intima of the smallest renal vessels, there was clinically extremely high blood pressure and marked cardiac hypertrophy.

In these cases the great majority of the glomeruli were normal or almost so and presumably capable of excellent function, and the tubules showed little pathologic change. These cases, in spite of the very high blood pressure, exhibited normal renal function so long as cardiac compensation remained good. This was truly a vascular disease. Death occurred usually from cardiac decompensation or cerebral hemorrhage. The "combination form" of vascular nephritis was that in which in addition to the arteriosclerosis of the type just described, there developed, while cardiac compensation was still good, signs of renal insufficiency often terminating in uremia. Histologically this form showed extensive glomerular atrophy, hyalinization or fibrosis secondary to the primary arteriosclerotic change.

It is thus seen that there has been a growing tendency to interpret the pathologic change of a considerable number of contracted kidneys, so-called chronic interstitial nephritis, as primarily vascular. The origin of the chronic vascular changes so characteristic of these forms of kidney

disease has been stated as unknown by most writers, except for vague references to metabolic toxemias and Volhard's [12] suggestion of a spastic contraction of the small kidney arteries comparable to bronchiole smooth muscle spasm in asthma. A great amount of experimental work has been done attempting to reproduce in animals the characteristic pathologic change of primary contracted kidney of man.[13] Kidney damage has been produced in a variety of ways, leading chiefly to glomerular and tubular damage with secondary chronic inflammatory and fibrotic changes, but the characteristic vascular pathologic change has generally been lacking. The conception of the origin of these vascular changes in specific acute infectious arteritis or periarteritis nodosa, as presented by the case reported in this paper, may explain the difficulty of experimental reproduction. The streptococcus or other organism responsible for renal periarteritis nodosa is not easily grown in culture and probably is highly adapted to the human environment.

SUMMARY

1. Renal periarteritis nodosa is considered as an acute vascular nephritis leading in nonfatal cases to chronic renal arteriosclerosis and chronic vascular nephritis.

2. The term "chronic vascular nephritis" is applied to a large group of contracted kidneys in which the primary pathologic condition is in the arteries and the secondary pathologic change is due to gradual arterial obliteration.

12. Volhard, F.: Die Doppelseitigen haemotogenen Nierenkrankungen, Berlin, 1918.

13. Leiter, L.: Experimental Chronic Glomerulonephritis, Arch. Int. Med. **33**:611 (May) 1924.

WHEN DO LUNGS RETURN TO NORMAL FOLLOWING EXPOSURE TO WAR GASES?*

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The use of toxic gases during the recent World War introduced a new subject in medicine. The clinical effects and the acute pathologic lesions of these gases have now been quite thoroughly investigated, but very little is known concerning what chronic lesions may remain after all symptoms have subsided. The need for further knowledge on this subject is apparent to all concerned in the care of sick veterans or in the fixing of compensation for soldiers who have been gassed. Because there is little opportunity to gain this knowledge from studies on soldiers who were the victims of gas attacks, this series of experiments on animals has been carried out.

We have attempted to determine whether pathologic lesions persist in the lungs of dogs which have been gassed but which have recovered from all symptoms. We had hoped to study the pathologic physiology as well as the pathologic anatomy of these animals, but have been prevented from doing so by our inability to measure the working capacity of dogs by means of the treadmill or other device.

METHOD

All the dogs used were gassed with the minimal lethal dose of the gas in question. Some dogs survived this dose, but were sick for periods of time varying from a few days to a month. They were considered recovered after their temperature, pulse and respiration had become normal and all symptoms, such as coughing, depression and general lack of well being, had disappeared. These dogs were then kept in kennels having large yards, so that they could exercise and live under approximately normal conditions. They were killed at varying intervals of time after recovery and carefully studied in order to see if any pathologic lesions remained as a result of the gassing.

Various methods of killing animals that had recovered were tried in order to find a method which in itself would cause the least variation from the normal in tissue structure. At first we used injections of potassium cyanid into the heart, but it was found that this caused an extreme grade of congestion in the lungs. Chloroform also caused lung congestion and, besides, theoretical objections might be raised to the

* From the Pathological Section, Medical Research Division, Edgewood Arsenal.

use of any inhaled vapor. Shooting or a blow on the head caused confusing hemorrhages and objectionable agonal struggles. We finally adopted the method of injecting a saturated solution of magnesium sulphate into the heart, and have used it in practically all our experiments. This causes very little congestion of the lungs, even when injected into the right side of the heart. To avoid this entirely, we have as a routine procedure injected 10 c.c. of the solution into the left ventricle. This makes it necessary for the solution to travel through the entire systemic circulation before it reaches the lungs, where it produces little or no change. Death is practically instantaneous without agonal convulsions, which, if severe enough, are in themselves often the cause of hemorrhage. We have therefore an ideal method of producing death, as it does not alter the pathologic condition that existed in the living animal.

The lungs of dogs are rather delicate mechanisms and will permit of very little handling without structural alterations. We were therefore troubled in our early work with lesions that we felt must be artefacts. Atelectasis was the main lesion thus encountered, and was almost constantly encountered in spite of the most careful handling, and the use of very sharp knives in cutting the blocks for fixation. In order to avoid this difficulty, we have employed the method of removing both lungs with the trachea and running Zenker's fluid into the trachea until the lungs are normally expanded, and at the same time immersing them in a vessel containing Zenker's fluid. By this method fixation is complete and almost instantaneous, and after the lungs have remained in Zenker's fluid a sufficient time, blocks can be cut for section without danger of producing artefacts. It is best to run the fixative into the trachea until the lungs are pretty well distended before immersing them in the vessel containing the fixative; otherwise the subpleural portions will be fixed in their collapsed state before the intratracheally injected fixative reaches these parts, and under the microscope these regions give the appearance of marginal atelectasis. By carefully carrying out this method, however, it is possible to bring the danger of artefacts to a minimum.

We have studied principally dogs which had recovered from the effects of phosgene, mustard, lewisite, chlorin, chlorpicrin, and methyldichlorarsin. There is a total of 313 dogs in the series. The effects of each gas are considered separately below.

The dogs that recovered and later died in the kennels and those which were killed in the kennels by other dogs have been included in the series along with those which were killed at definite stated intervals after the cessation of symptoms. This has been done for the sake of completeness and in order to be sure not to vitiate our results. Most of the

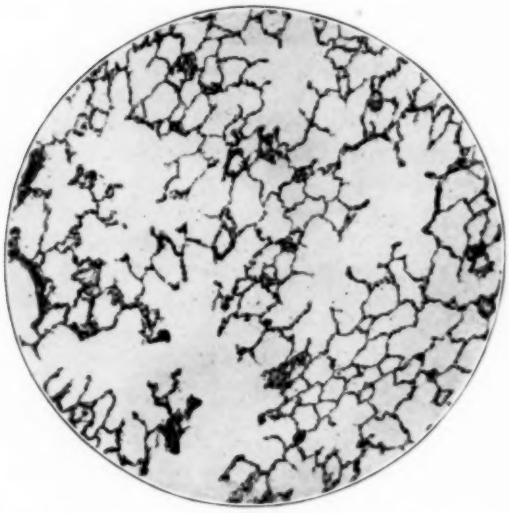

Fig. 1.—Normal lungs in dog two weeks after recovery from phosgene.

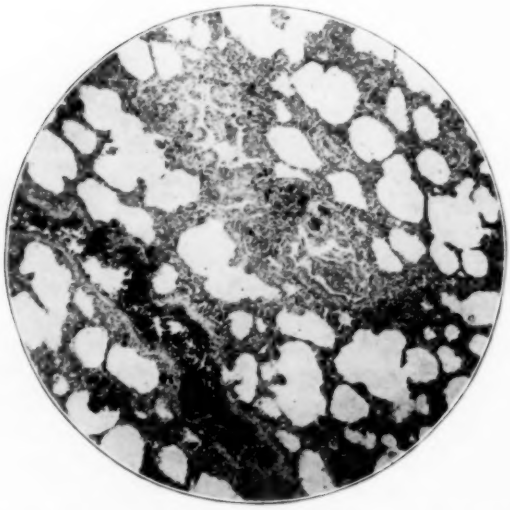

Fig. 2.—Bronchi plugged with exudate, desquamated epithelial cells and débris in dog that died three weeks after recovery from phosgene.

dogs dying in the kennels died of some acute lung condition which may or may not have had any relation to the previous gassing. Of the ordinary run of stock dogs kept in the kennels, about 10 per cent. die or are killed in the course of a year. It will be seen that the percentage for our dogs that recovered from gassing is much higher (28.1 per cent.). That there is some relationship betwen previous gassing and death in the kennels is thus clearly established. Most of this high mortality rate, however, occurred within the first two months after recovery from gassing, 39.8 per cent. of the total number of recovered dogs in the

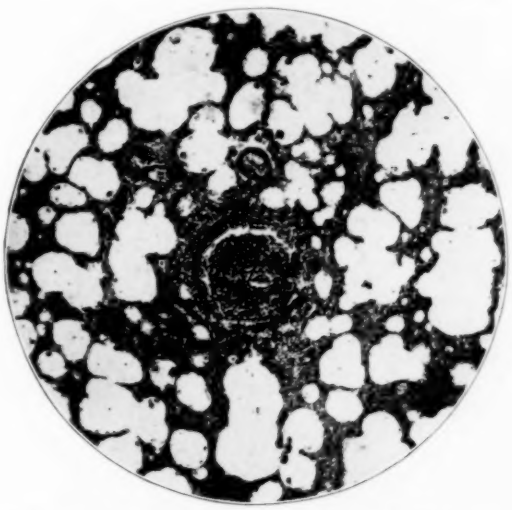

Fig. 3.—Obliterative bronchiolitis in dog that was killed by other dogs three weeks after recovery from phosgene.

kennels dying within the first month, 33⅓ per cent. during the second month, and only 16.4 per cent. during the period from the end of the second month to the end of the fifteenth month.

PHOSGENE

Ninety-five dogs that recovered from gassing with phosgene were studied. Sixty-one of these were killed with magnesium sulphate at intervals varying from two weeks to fifteen months after recovery. Thirty-four died or were killed in the kennels at intervals of from one week to eight months after recovery.

Gross Pathology.—Sixty-eight of the series appeared normal in the gross. Of the remaining twenty-seven, three showed empyema and

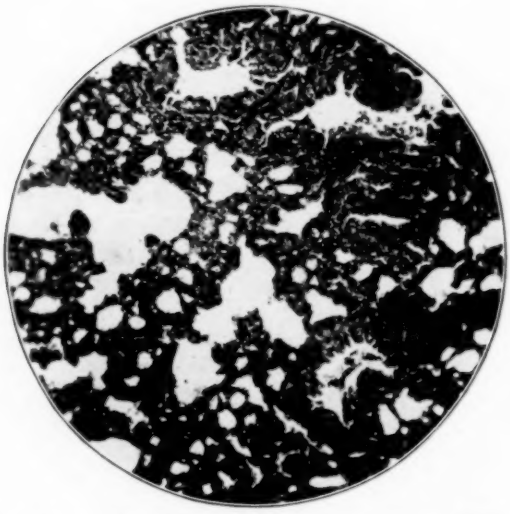

Fig. 4.—Chronic bronchitis and partial atelectasis due to plugged bronchi in a dog killed five weeks after recovery from phosgene.

Fig. 5.—Patch of organization in dog killed eighteen weeks after recovery from phosgene.

two pneumonia. The others had such lesions as congestion, hemorrhage, edema and emphysema in varying degrees of intensity. Most of these gross lesions were found in dogs that died.

Microscopic Findings.—In three of ten dogs that were killed or died two weeks after recovery, the lungs were normal microscopically. There was no definite point in the series at which it could be said that all pathologic lesions had disappeared, and the majority of the lungs were normal. However, of the ninety-five dogs studied, in twenty-one the lungs were normal, and in twenty-four more were almost normal, having only small areas in which there were lesions of minor degree. Of the

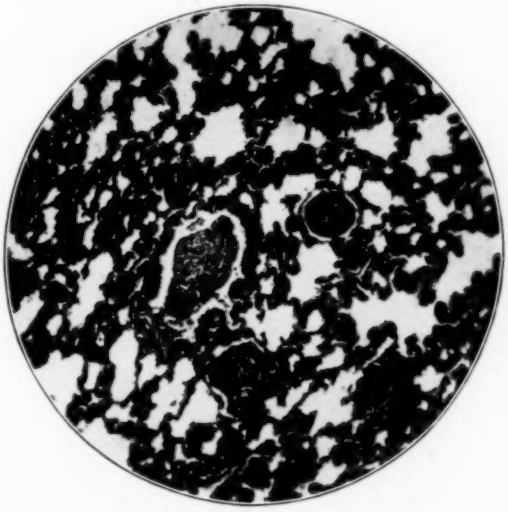

Fig. 6.—Chronic obliterative bronchiolitis in dog that died eight months after apparent recovery from phosgene.

lesions encountered in the early weeks after recovery, the predominating one was a plugging of the bronchi with desquamated epithelial cells and débris and atelectasis of the adjacent lung tissue. This gradually gave way to obliterative bronchiolitis and small patches of organization as the principal lesions. Small hemorrhages were often found around the patches of organization. On the whole, however, the appearance of the lungs took on a more and more normal aspect as the time from the date of recovery increased. As would be expected, a much larger area in which there was pathologic change was encountered in dogs dying in the kennels than in those killed with magnesium sulphate (Figs. 1 to 6).

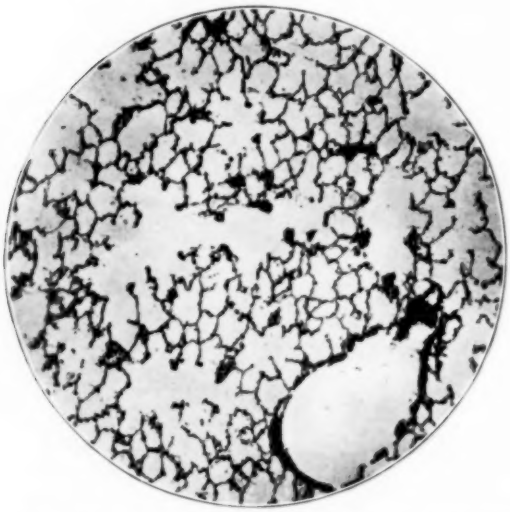

Fig. 7.—Normal lungs in dog killed at time of recovery after being sick for four weeks from mustard.

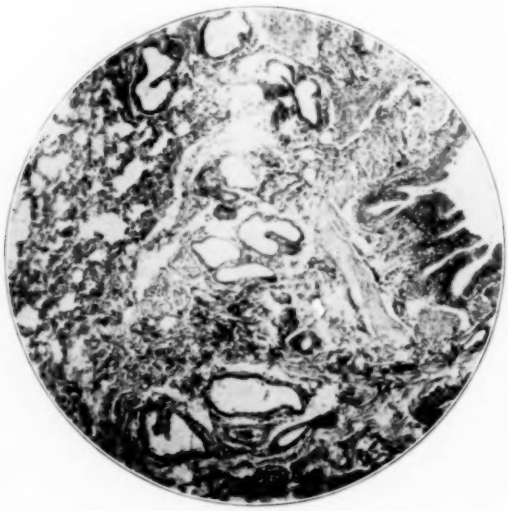

Fig. 8.—Hypertrophied bronchial epithelium and dilated mucous glands in wall of bronchus of dog killed six weeks after recovery from mustard.

MUSTARD

There were fifty-eight dogs in the series given mustard gas. Of these, forty were killed with magnesium sulphate at intervals varying from the actual time of recovery to eight months after recovery. Eighteen died or were killed in the kennels at intervals of from one week to nine months after recovery.

Gross Pathology.—Forty-six of the fifty-eight dogs studied appeared normal in the gross. Of the remaining twelve, one had pneumonia. The others showed such lesions as congestion, hemorrhage, edema, atelectasis and emphysema. As in the case of phosgene, nearly all the gross lesions occurred in dogs that died.

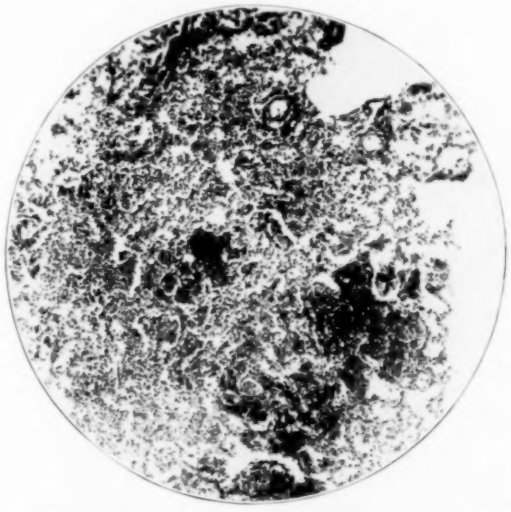

Fig. 9.—Normal lungs except for few patches of organization surrounded by minute areas of bronchopneumonia in dog that never really recovered from effects of mustard gas. The dog was discharged from the hospital at the end of twenty weeks still having a hoarse cough and bad eyes.

Microscopic Findings.—The only dog killed at the actual time of recovery had lungs that were entirely normal. Of eleven dogs killed from two to three weeks after recovery, three had normal lungs. Of six dogs killed four weeks after recovery, four had normal lungs. Of six dogs killed six weeks after recovery, three had normal lungs. From eight weeks on practically the only lesions encountered were small patches of organization. The early lesions, as in the dogs that recovered from phosgene, consisted principally of the plugging of bronchi with débris and atelectasis of the adjacent lung tissue. In most cases these

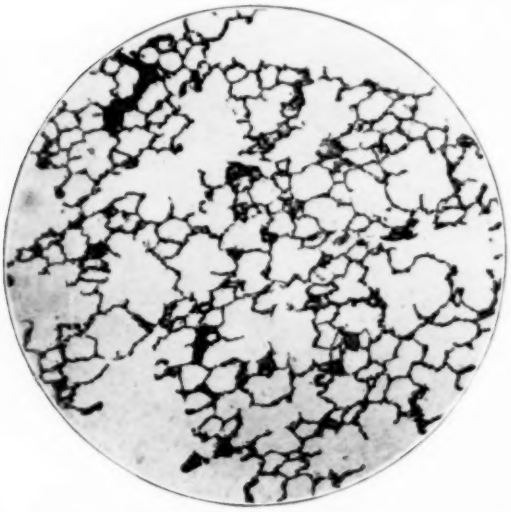

Fig. 10. Normal lungs of dog killed five weeks after recovery from lewisite.

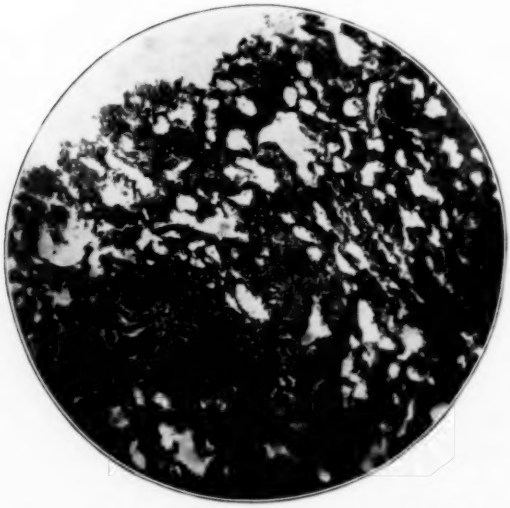

Fig. 11.—Plugging of bronchus with desquamated epithelial cells and débris in dog that died ten weeks after recovery from lewisite.

lesions occupied very limited areas of lung tissue. Occasionally, areas of chronic inflammatory reaction were encountered. Congestion, hemorrhage and edema were often found in the dogs dying in the kennels (Figs. 7 to 9).

LEWISITE

There was a total of sixty dogs in the series given lewisite. Forty-five of these were killed with magnesium sulphate at intervals varying from two to twenty-one weeks after recovery. Fifteen died or were killed in the kennels at intervals of from one to ten weeks after recovery.

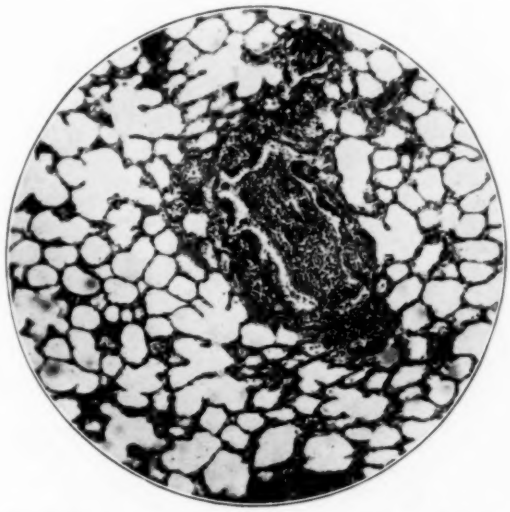

Fig. 12.—Organizing obliterative bronchiolitis in dog that died ten weeks after recovery from lewisite.

Gross Pathology.—Forty-five of the sixty dogs studied appeared normal in the gross. These were the dogs killed. Of those dying, fifteen in number, four had pneumonia and one bronchitis. The others showed varying degrees of congestion, hemorrhage, edema, atelectasis and emphysema.

Microscopic Findings.—Lesions similar to those encountered in the early weeks after recovery in the phosgene and mustard series were found in this series also during the first five weeks. The sixth week in this series, however, marks a definite point at which the pathologic lesions disappear, except for a few chronic changes similar to those spoken of above, and the more acute changes found in those dogs which die in the kennels (Figs. 10 to 12).

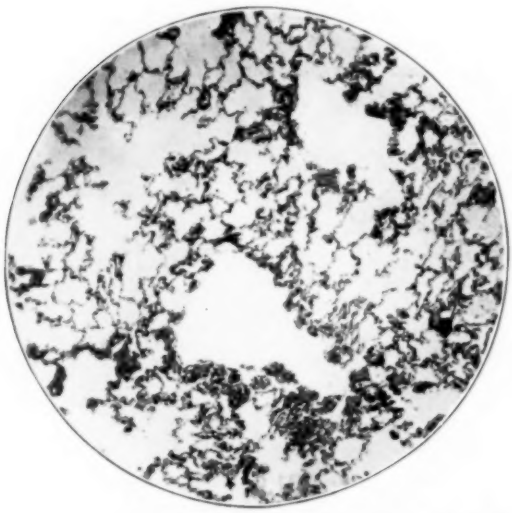

Fig. 13.—Marginal atelectasis and minute hemorrhages in almost normal lungs in dog killed one week after recovery from chlorin.

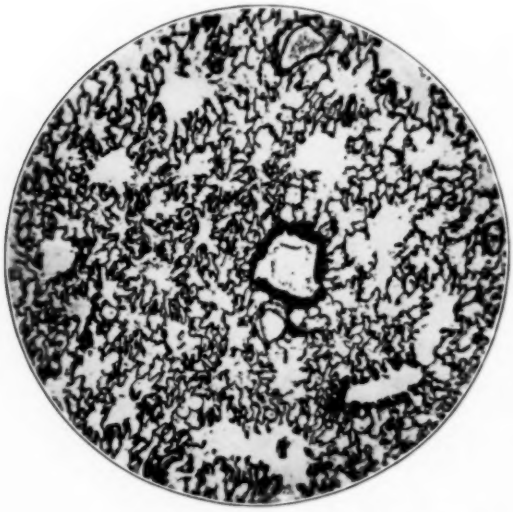

Fig. 14.—Normal lungs in dog killed four weeks after recovery from chlorpicrin.

CHLORIN

There were only eleven dogs in the series given chlorin—too small a number from which to draw any definite conclusions. Seven of the eleven were killed with magnesium sulphate at intervals varying from one to twenty weeks after recovery. Four died or were killed in the kennels at intervals of from two to four weeks after recovery.

Gross Pathology.—Nine of the eleven showed no gross lesions. Of the remaining two, one had pneumonia and the other bronchitis. Both of these died in the kennels.

Microscopic Findings.—There were no absolutely normal lungs in the six dogs examined at necropsy in the first six weeks after recovery,

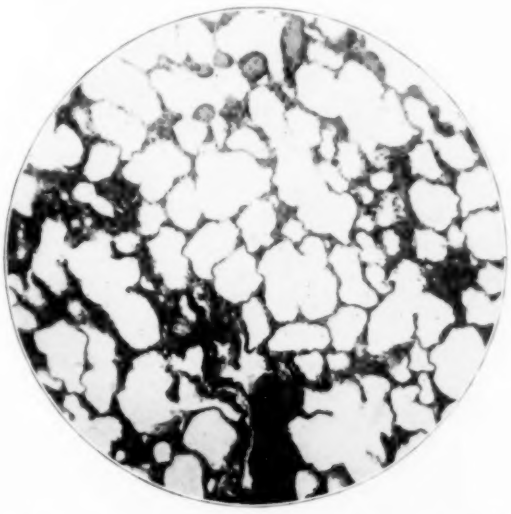

Fig. 15.—Small areas of organization in dog killed twenty-six weeks after recovery from chlorpicrin.

but this number included the four that died in the kennels. There were no necropsies on animals between six and thirteen weeks after recovery. Of the five examined at necropsy from thirteen to twenty weeks after recovery, three were normal. One examined at necropsy at fourteen weeks showed some old scars, and one at fifteen weeks had small areas of organization and hemorrhage (Fig. 13).

CHLORPICRIN

There were forty-eight dogs in the series given chlorpicrin. Eight died in the kennels, and forty were killed at intervals ranging from one to twenty-six weeks after apparent recovery.

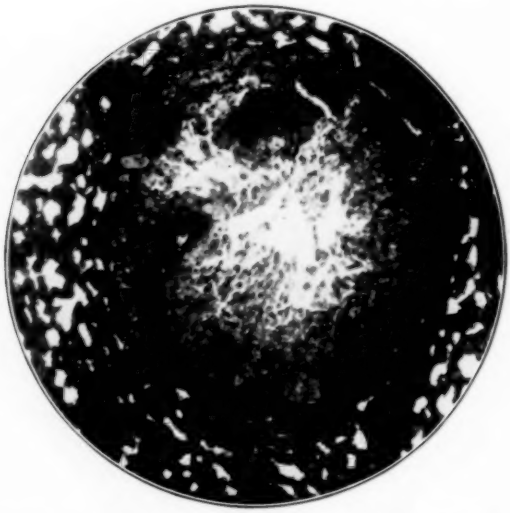

Fig. 16.—High magnification of chronic proliferative bronchiolitis in same lung as that shown in Figure 15.

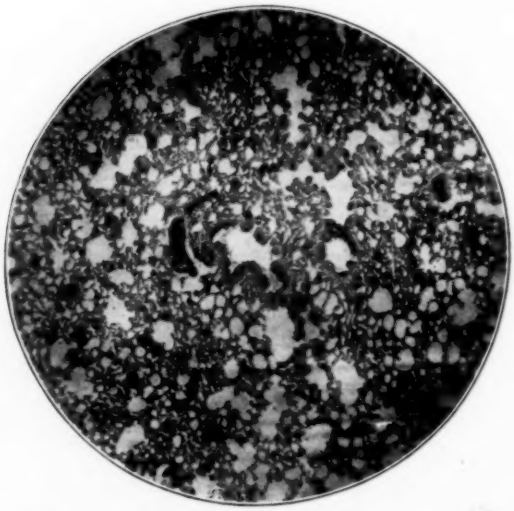

Fig. 17.—Partial return of lungs to normal in dog killed four weeks after recovery from methyldichlorarsin.

Gross Pathology.—There were no gross lesions, except for an occasional case of congestion, atelectasis or emphysema occurring in dogs that died.

Microscopic Findings.—The lungs of dogs killed from five to ten weeks after recovery showed an almost complete return to the normal. The dogs killed prior to this time showed about the same type of lesions as those occurring in the early weeks after recovery from the other gases. Dogs killed later showed occasional patches of organization and chronic bronchitis in some cases (Figs. 14 to 16).

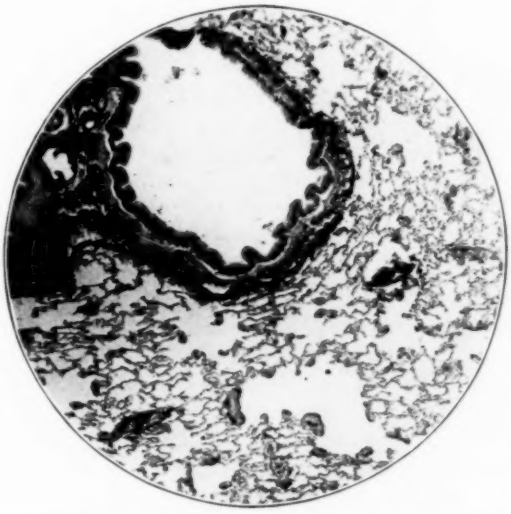

Fig. 18.—Normal lungs in dog killed eight weeks after recovery from methyldichlorarsin.

METHYLDICHLORARSIN

Forty-one dogs in the methyldichlorarsin series were examined at necropsy at intervals ranging from two to sixteen weeks after recovery. Nine of these died or were killed in the kennels. The rest were killed in the usual manner.

Gross Pathology.—In the thirty-two dogs sacrificed, there were no gross pathologic lesions. Of the remaining nine, one had pleurisy with adhesions, three had pneumonia, one organizing pneumonia, three purulent bronchitis, and one chronic peribronchitis.

Microscopic Findings.—Most of the animals had returned to normal within eight weeks after recovery, but some chronic changes were found up to sixteen weeks (Figs. 17 and 18).

SUMMARY

A number of dogs were exposed to approximately the lethal concentration of each of the following gases: phosgene, mustard, lewisite, chlorin, chlorpicrin and methyldichlorarsin. The dogs that recovered from the effects of the gases were discharged from observation on the cessation of symptoms, and were kept in the kennels to be killed at varying intervals of time from the date of recovery, in order that the pathologic lesions still remaining in the lungs might be studied. Of the recovered dogs, almost a third died in the kennels or were killed in the kennels by other dogs. This makes the mortality almost three times as high among the recovered gassed dogs as among the ordinary run of stock dogs in the kennels. It seems conclusive, therefore, that there is some connection between these deaths and the previous gassing of the animals. That no such parallel exists in men who were gassed during the World War is shown equally conclusively by the histories of men who were gassed during that conflict. The reason for the difference is probably that the soldiers had the best hospital care and treatment during the period of illness following the gassing, and equally good care for still further periods in convalescent camps, while the dogs received no treatment whatsoever, and after their discharge from the dog hospital, were exposed to rigors of weather and climate and the savage attacks of stronger dogs in the kennels.

The pathologic lesions found in the lungs of the dogs that died in the kennels were varied in number. In a few cases the lungs were normal, and such dogs probably died of starvation, being too weak or apathetic to compete for their food. In a number of other instances pneumonia was the cause of death. In the majority of cases, however, such lesions as congestion, hemorrhage, edema, plugging of the bronchi with débris and atelectasis were found.

The dogs that were killed at varying intervals after recovery may be divided into three groups as follows: (1) those in which the lungs were normal; (2) those which had more or less acute pulmonary lesions, and (3) those which showed chronic lesions. Normal lungs were found in a few dogs that were killed at the time of recovery, and the percentage of normal lungs gradually increased from this time to the end of the period of observation (fifteen months from date of recovery). However, the percentage of normal lungs in the first five to eight weeks after recovery was not very large, while after this period normal lungs were in the large majority. The more or less acute lesions that occurred in the first five to eight weeks after recovery consisted principally of edema, desquamation of alveolar epithelium, plugging of bronchi with débris, atelectasis, occasional patches of chronic inflammatory reaction and an occasional pneumonia. The chronic lesions occurred between the

period from five to eight weeks after the date of recovery and the end of the period of observation, and consisted principally of small patches of organization, often associated with minute hemorrhages, chronic bronchitis and peribronchitis and organizing obliterative bronchiolitis.

It should be made clear that the pathologic lesions encountered in the group of dogs that were sacrificed at various intervals of time after recovery were limited in extent and only discovered microscopically. In practically all of these dogs the lungs appeared normal in the gross. This is in sharp contrast with the dogs that died, in nearly all of which gross lesions were discovered at the necropsy table.

CONCLUSIONS

1. In the great majority of dogs gassed at lethal concentrations, no pathologic lesions can be demonstrated from two months to a year after recovery.

2. In a minority of instances, permanent lung damage is done; but this damage is not widespread, is generally confined to small areas, and is generally in the form of small patches of organization, thickening of the bronchial walls with loss of elasticity, or occasional closing of the bronchioles by organized exudate.

3. All such damage will ultimately result in fibrous tissue. This small amount of scar tissue can hardly affect the functional efficiency of the lungs.

4. Since the lungs of dogs are more delicate than those of human beings, it is reasonable to conclude that in the vast majority of surviving human patients, who were not gassed so severely and who receive infinitely better care in hospital, all lesions have disappeared within a short while after gassing, and that the small amount of fibrosis remaining in the minority of cases can hardly be a cause of serious disability.

FORMALDEHYD POISONING

WITH REPORT OF A FATAL CASE *

B. S. KLINE, M.D.

CLEVELAND

Although formaldehyd has been extensively used in a number of industries since its discovery in 1867 by Von Hoffmann, there are on record, including the one at Mt. Sinai Hospital reported here, only twenty-seven cases of formaldehyd poisoning.

Of these twelve patients (seven males and five females) died in from twenty or thirty minutes to four weeks. In the case of the males, formaldehyd was taken by mistake for whisky or water. In the case of the females, it was taken with suicidal intent.

The amount of formaldehyd ingested in the fatal cases varied from a few drops to 3 ounces (89 c.c.) of concentrated solution. The largest amount from which a patient recovered (case of Hale) was 120 c.c. of concentrated commercial formaldehyd.

Below is a summary of the clinical and pathologic records of the fatal cases. The first four are quoted from MacLachlan,[1] who reviewed the literature to 1909 and in his report summarized the clinical features of formaldehyd poisoning.

REPORT OF CASES

CASE 1 (Reported by Bock[2] in 1899).—A man, aged 26, took 3 ounces (89 c.c.) of solution of formaldehyd U. S. P. (formalin 100 per cent.) and died in thirty-two hours.

Clinical Course.—The patient immediately vomited blood tinged mucus and had severe epigastric pain. Demulcents and apomorphin were given at once, resulting in free emesis. The patient continued weak and vomited repeatedly. Sixteen hours later the pulse first weakened. The patient remained in statu quo until the twenty-ninth hour, when the heart failed rapidly. At the thirty-second hour, there was cyanosis, coma and then death.

Pathology.—The lower end of the esophagus showed marked erosion. The stomach wall and duodenum were very much congested and cut like leather. Microscopic examination was not made. Other findings were not abnormal.

CASE 2 (Reported by Levison[3] in 1904).—A man, aged 60, took 3 ounces (89 c.c.) of solution of formaldehyd U. S. P. (formalin 100 per cent.) and died in twenty-nine minutes.

Clinical Course.—The patient was found writhing in pain and unable to speak. He did not vomit even after three-tenths grain (0.018 gm.) of apomorphin. Lavage was attempted, but the tube could not be passed on account of spasm of the pharynx. The patient died of cardiac failure in twenty-nine minutes after taking the poison.

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* From the Laboratory Service of Mt. Sinai Hospital.

1. MacLachlan: Cleveland M. J. **8**:606, 1909.
2. Bock: Fort Wayne M. J. **19**:249, 1899.
3. Levison, L. A.: J. A. M. A. **42**:1492 (June 4) 1904.

Pathology.—The esophagus, stomach and small intestine were literally "hardened."

CASE 3 (Reported by Bose[4] in 1905).—A man, aged 47, took 3 ounces (89 c.c.) of solution of formaldehyd U. S. P. (formalin 100 per cent.) and died in thirteen hours.

Clinical Course.—The patient was found shortly after taking the poison, unable to speak, with hands on abdomen and apparently in great pain. He did not vomit before admission to the hospital. After a lavage he was able to talk rationally. He started to vomit almost at once and continued all that night, the vomitus being blood tinged. The patient gradually sank but developed no other symptoms and died the next day, thirteen hours after the ingestion of the poison.

Pathology.—The esophageal and gastric mucosa was intensely congested, as was that of the small and large intestines. Some slight changes in the parenchymatous organs were noted.

CASE 4 (Reported by Palmer[5] in 1906).—A man, aged 29, took about 7½ ounces (222 c.c.) of solution of formaldehyd U. S. P. (formalin percentage not given), and died in three days.

Clinical Course.—Shortly following ingestion, the patient experienced intense abdominal pain and collapsed. When admitted to the hospital, he was tender over the epigastrium. He vomited blood tinged fluid, was slightly delirious and had a marked feeling of constriction of the throat. He was given a dilute solution of ammonia followed by demulcents. The next day his mind was wandering but he was in no special pain. Two days later, he became markedly delirious, noisy, and at times maniacal. During one of these attacks, his pulse failed, his breathing became shallow, and his heart stopped.

Pathology.—The blood everywhere was found dark colored and fluid. The mucous membrane of the lower end of the esophagus and the gastric mucosa were tanned, and the parenchymatous organs were somewhat congested.

CASE 5 (Reported by Ely[6] in 1910).—A boy, aged 3 years, took a few drops of solution of formaldehyd U. S. P. (formalin 100 per cent.) and died in about forty-eight hours.

Clinical Course.—The patient was immediately seized with a paroxysm of coughing and choking, but the attack soon ceased. The child's mouth was rinsed out thoroughly with water, and he was soon at play as if nothing had happened.

On the next day, there was a hoarse laryngeal cough with accelerated and labored breathing. The pulse and temperature were normal and in every respect the child seemed to be in perfect health. A laryngeal application of epinephrin was employed with temporary benefit. Inhalations of steam were advised, and frequent teaspoonful doses of olive oil were ordered to allay any pharyngeal or esophageal irritation. Fifteen hours later, the child was deeply cyanosed and showed every sign of laryngeal obstruction. Repeated applications of epinephrin were made and the breathing became somewhat easier, but during the night, eight hours after admission to the hospital, the child died.

Pathology.—Marked thickening of the mucous and submucous coats of the epiglottis, larynx and trachea, with a superficial necrosis that extended to the bifurcation of the trachea were found. The esophagus showed no pathologic changes, nor was there evidence of destruction of the mucosa of the mouth and pharynx.

4. Bose: Indian M. Gaz. **40**:139, 1905.
5. Palmer: Australian M. Gaz. **25**:188, 1905.
6. Ely, F. A.: J. A. M. A. **54**:1140 (April 2) 1910.

Case 6 (Reported by Watt[7] in 1912).—A man, aged 63, took 1 ounce (30 c.c.) of solution of formaldehyd U. S. P. (formalin 100 per cent.) and died in two and one-half hours.

Clinical Course.—The patient left home about 8:00 a. m. without taking any breakfast. He was seen about 9:15 a. m., when near a well in a public park, to become rapidly ill. He staggered, doubled up over a low railing and retched viscid mucoid material. He was put on a seat and soon was unconscious with his body stretched out and his head bent back over the seat. The man was supposed by bystanders to be in a "fit," and was laid out on the grass with his collar loosened. He was breathing "heavily," with chest heaving and eyes rolling, and was perspiring moderately. Accounts differ about pallor or flushing of the face. No convulsions or twitchings of the muscles were noticed nor was any attention drawn to coldness of the hands and face. After being unconscious for about fifteen minutes, he gradually became conscious. The

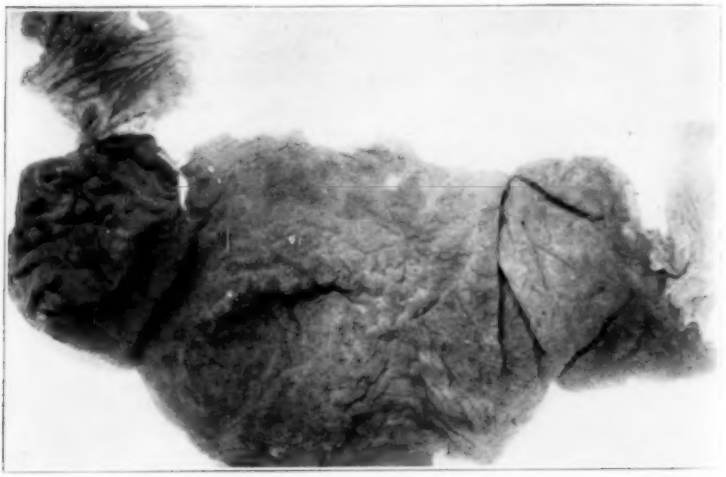

Fig. 1.—Esophagus, stomach and duodenum after formaldehyd poisoning of three hours' duration.

man did not again vomit, but was now suffering very severe abdominal pain. This caused him at intervals to double up almost on his hands and knees. There was some froth about the mouth, but no discoloration of the lips or mouth was noted. He staggered along with assistance for about 100 yards. He then fell to the ground writhing with pain, and relapsed into unconsciousness, from which he did not again emerge.

At 11:00 a. m. he was admitted to the hospital, unconscious, collapsed and almost pulseless. The skin was pale, cold and clammy. The mouth was opened with a gag but showed no discoloration and did not smell of formaldehyd. All reflexes were absent on admission except the corneal reflex. This also was lost in a few minutes, and respirations stopped. The stomach was washed out, stimulants were given and artificial respiration applied, but death ocurred at 11:53 a. m.

Pathology.—No necropsy was done.

7. Watt: Brit. M. J. **2**:350, 1912.

Case 7 (Reported by Moorhead[8] in 1912).—A man, aged 30, took 3 ounces (89 c.c.) of solution of formaldehyd U. S. P., 10 per cent., and died in four weeks.

Clinical Course.—The patient was admitted to the hospital suffering from acute perforative appendicitis. An operation was performed immediately, and a gangrenous appendix was found along with diffuse suppurative peritonitis. Improvement after the operation was rapid and in a week the temperature had almost reached normal, though there was a profuse local discharge of pus. When in this condition, the patient went to a cupboard in the ward and drank the formaldehyd from a bottle there. About five minutes later, he was quite unconscious. The face was strongly flushed, the breathing stertorous, the pulse 90 to the minute, but steady and rather full. There was no discoloration of the lips or mouth, but there was a strong odor of formaldehyd from the breath. The pupils were dilated; conjunctival reflex was present, and the conjunctivae were injected. The skin over the chest and abdomen was pale and moist.

A stomach tube was passed and the stomach was washed out with strong ammonium acetate. The first washing smelled most strongly of formaldehyd, in fact, overpoweringly so, and contained much altered blood. The washing was continued until no smell of formaldehyd could be detected from the water that siphoned back from the stomach. Before this stage was reached, however, the patient recovered consciousness; in fact, he began to revive as soon as the large quantity of formaldehyd had been evacuated. He slept well that night and the next day he seemed almost completely recovered, except for some slight pain in the throat. No abdominal pain whatsoever was complained of. The first motions after the incident were tarry and contained a little mucus, but later, though fluid, were free of blood.

The subsequent history was unfortunate; burrowing abscesses formed in the neighborhood of the appendix wound and general septicemia ensued. Death took place five weeks after admission.

Pathology.—Patches of fat necrosis were found in the abdomen; the interior of the esophagus and stomach were extremely corroded, the most marked corrosion being found close to the pylorus. No signs of irritation were found in the duodenum or elsewhere in the alimentary canal. Apart from the changes commonly found in the organs in fatal cases of septicemia, nothing else abnormal was detected.

Case 8 (Reported by Shaposhnikoff[9] in 1912).—A woman, aged 21, took 30 c.c. of solution of formaldehyd U. S. P. (formalin 100 per cent.) and died in nine days.

Clinical Course.—The patient, not knowing that she would become unconscious, lay without help until the next morning after she had taken the dose. She then had a severe burning in the abdomen and in the throat; she cried for help. She was brought to the hospital. In a short time, she had her stomach washed out. A strong odor of formaldehyd came from her mouth. On examination there was marked hyperemia around the uvula and, in a few places, small white areas without epithelium. Laryngoscopy showed widespread hyperemia. There was shortness of breath. The pulse was 126; the temperature, 38.5 C. Lungs and heart were negative. There were tracheal rhonchi. The pain in the abdomen decreased. The urine in output, color and odor was normal; there was no albumin. She was given soda water and milk. Three days after admission, she was fully conscious; the pulse was 120; the temperature, 39.5 C. Pneumonia was found in the left upper and lower lobes. The urine, 1,000 c.c., contained albumin. On the fourth day, there was pneumonia on the other side. The temperature was 40.8 C.; the sputum was

8. Moorhead: Brit. M. J. **2**:1470, 1912.
9. Shaposhnikoff: Terap. Obozr., Odessa, **5**:537, 1912.

gangrenous and had a putrid odor; the pulse was 130. Heart sounds were very weak; there were no murmurs. The amount of the urine was 800 c.c. The patient was in marked stupor.

On the ninth day after admission, there was a marked putrid odor of the mouth. She could not be aroused, and died during the day in asphyxia.

Pathology.—The diagnosis was diffuse bilateral bronchopneumonia. No report of the abdominal organs or esophagus was made.

Case 9 (Observed by Christie[10] in 1914).—A woman, aged 33, took an unknown quantity of solution of formaldehyd U. S. P. (formalin percentage unknown), and died in nine and one-half hours.

Clinical Course.—The patient was admitted shortly after drinking solution of formaldehyd (formalin percentage and quantity unknown). There was con-

Fig. 2.—Edema of the submucosa and muscle of the esophagus after formaldehyd poisoning of three hours' duration.

siderable abdominal distress. The pulse was not obtainable at the wrists. The temperature rose steadily to 101.5 F. just before death.

Three and one-half hours after admission, the patient was extremely nervous and flighty.

Fifteen minutes before death, no pulse was obtained at the wrists. There was extreme cyanosis and marked restlessness.

A heavy trace of albumin and granular casts were noted in the urine.

Pathology.—No necropsy was done.

Case 10 (Reported by DeRechter[11] in 1914).—A woman, aged (?), took 1½ ounces (45 c.c.) of solution of formaldehyd U. S. P. (formalin 32 per cent.) and died in between twenty and thirty minutes.

Clinical Course.—The patient had immediate pain and vomited black, bloody masses; the pulse was feeble. She died in between twenty and thirty minutes.

10. Christie: Personal communication from the author. The patient died in Lakeside Hospital, Cleveland, in 1914.

11. DeRechter: Arch. Int. de Med. Legale **5**:44, 1914.

Pathology.—The hardening to a leathery consistency of the mucosa of the tongue, cheeks, esophagus, stomach and the uppermost meter of the small intestine was observed. There also was hardening of portions of organs neighboring the stomach (lung, spleen and pancreas).

Case 11 (Reported by Marx[12] in 1919).—A woman, aged 27, took 4 ounces (118 c.c.) of solution of formaldehyd U. S. P. (formalin 47 per cent.) and died in sixty-two hours.

Clinical Course.—The patient had pain in the chest and epigastrium, followed in fifteen minutes by vomiting. These symptoms continued for a few hours. The gastric lavage was followed by dyspnea, cyanosis of the face and hands and a feeble pulse. There was no loss of consciousness. There was no improvement of the pulse following stimulation.

No disturbance of micturition occurred. The temperature was normal for the first few days, rising to 100 F. shortly before death.

Pathology.—Marked hyperemia and edema of the brain and lungs and ecchymosis of the pleural epicardium were present; 200 c.c. of purulent exudate was observed in the abdominal cavity. No abnormalities of the mucosa of the

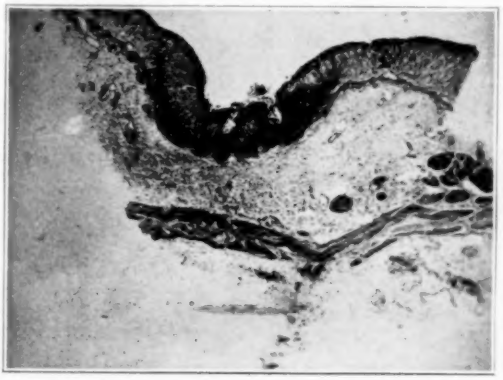

Fig. 3.—Early acute inflammation of stomach, showing linear ulcers, hemorrhage and edema, after formalydehyd poisoning of three hours' duration.

lips, floor of the mouth or cheeks were seen. That of the pharynx and larynx was injected but intact. The esophageal mucosa was grayish red, dry and somewhat wrinkled, with changes most marked toward the stomach. The stomach, contracted and grayish-red, contained about 100 c.c. of brown matter with intermingled flecks of sloughed mucosa. The mucosa of the stomach was markedly tumefied and on the crests of the folds was converted into a friable eschar. In the region of the pylorus, the sloughs were white. These peeled off readily. The underlying areas were grayish red. In portions of the fundus, the mucosa in places was completely absent. The stomach wall was everywhere thickened and infiltrated by dark blood.

Microscopic Examination.—Parenchymatous and fatty degeneration of the liver parenchyma was observed with degeneration of the kidneys and patchy necrosis of the tubal epithelium, especially in the region of the pyramids, with marked hyperemia. The heart muscle showed no abnormalities. In the lower portion of the esophagus in places, there was loss of surface epithelium with necrosis of the tunica propria in these areas. In other places the epithelium

12. Marx: Med. Klin. **15**:925, 1919.

was perfectly intact. The stomach showed marked alteration. The entire surface epithelium was necrotic. In many places the necrosis reached the muscularis mucosae. The submucosa showed extensive hemorrhage and small mononuclear round cell infiltration reaching to the serosa.

CASE 12 (author's case).—A woman, aged 33, took from 2½ to 3 ounces (74 to 89 c.c.) of solution of formaldehyd U. S. P. (formalin 100 per cent.) and died in three hours.

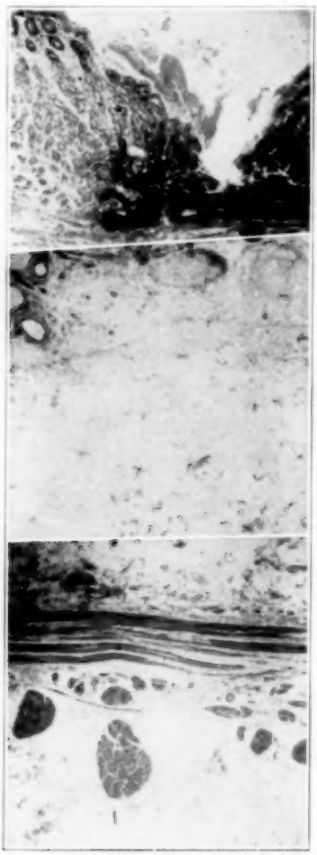

Fig. 4.—Linear ulceration, hemorrhage and marked edema of stomach after formaldehyd poisoning of three hours' duration.

Clinical Course.—The patient, who was unconscious, was brought to the hospital forty-five minutes after drinking the formaldehyd.

She was a slender, white woman, unconscious and in shock. Her pulse was thready; her eyes were half opened; the conjunctivae were injected, and the skin was cold and clammy. Gastric lavage was performed. Stimulants were given intravenously. The patient did not respond and died three hours after the ingestion of the formaldehyd.

Pathology.—Necropsy was performed eighteen hours postmortem. The anatomic diagnosis was early acute gastritis (marked) following ingestion of formaldehyd solution; early acute enteritis (moderate); acute cardiac dilatation (right) moderate; terminal pulmonary edema (slight), and healed peritoneal adhesions. The probable cause of death was shock following formaldehyd poisoning, with marked early acute gastritis and moderate early enteritis.

Of interest in the necropsy were the following points: There were a few hemorrhages observed in the mucous membrane of the inner surface of the lips. The mucosa of the esophagus throughout was whitish, perhaps slightly thickened. The submucosa showed some thickening by clear fluid. The stomach was several times the average size, contained about a liter of partially digested food and brownish, somewhat oily fluid, which on distillation gave the typical reaction for formaldehyd. The walls were greatly thickened, from 5 to 10 mm. This was most marked in the mucosa and submucosa, especially near the cardia, which was watery and gelatinous in appearance. The mucosa had a pigskin appearance with linear ulcerations and an almost diffuse dull reddish appearance suggesting hemorrhage. The duodenum showed moderate swelling, injection

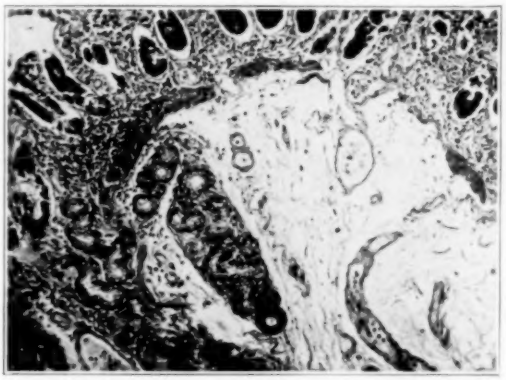

Fig. 5.—Early inflammation with marked edema of duodenum after formaldehyd poisoning of three hours' duration.

and hemorrhage of the mucosa. The cecum and ascending colon also showed some injection. The remainder of the colon and rectum showed no appreciable abnormalities.

Microscopic Description.—Section of the esophagus showed an intact surface epithelium. The submucosa and to a less extent the muscle showed a moderate amount of amorphous pink stained material separating the fixed tissue. The blood vessels were engorged and contained somewhat more numerous nucleated cells than normal. There were a few wandering cells in the regional fixed tissue.

One section of the stomach showed in two places superficial ulceration of the mucosa a few hundred to 500 microns in width, extending only half way through the mucosa. About these ulcers there was marked infiltration of the tissues by red blood cells (not laked). In the base of each there were abundant wandering cells. The striking change in the mucosa was apparently the marked edema. The mucosa was 2.5 mm. in width. The blood vessels were everywhere engorged. There were areas of hemorrhage and a moderate number of wandering cells in the loose stroma. The hemorrhage about the ulcerations continued for a small distance into the submucosa. This coat was strikingly

edematous apparently, in places 4 mm. in width. The muscle and serosa showed a similar picture of marked edema. The blood vessels were somewhat engorged. There were no wandering cells in the fixed tissue of the outer coats. A second section, from 7 to 8 mm. in width, showed a similar picture with areas of linear ulceration, one of which continued to the submucosa. The blood in the mucosa was in striking contrast to that in the serosa. In the former position the red cells were intact; in the latter they were laked. Both sections showed striking engorgement of the vessels in the inner portion of the submucosa.

Section of the duodenum showed a picture of moderate edema of the mucosa and marked edema of the submucosa. The engorged blood vessels in the latter coat, with the blood in great part, was laked, and there were a moderate number of wandering cells in the mucosa and submucosa. The innermost portion of the mucosa, especially of the villi, was in great part necrotic, with considerable separation of the tissue by amorphous, pink stained material. The picture resembled postmortem change.

Section of the jejunum showed considerable desquamation of the surface epithelium. There was slight edema of the mucosa and apparently moderate edema of the submucosa. A number of blood vessels showed within and about them a moderate number of wandering cells. The blood in great part was laked.

SUMMARY OF PATHOLOGIC CHANGES IN FATAL CASES

Of the twelve fatal cases, ten came to necropsy. In all these, the changes were most marked in the lower esophagus and to an even greater extent in the stomach. The changes in these organs varied from simple hardening of the tissues to extreme corrosion. Frequently, marked congestion and edema were present with areas of erosion and of hemorrhage. Occasionally similar but less marked changes were observed in the duodenum and even jejunum. The remainder of the alimentary canal rarely showed any abnormality. In cases continuing thirteen hours or longer after ingestion of the formaldehyd, degenerative changes in the parenchymatous organs were noted, varying from slight cloudy swelling to fatty degeneration and even patchy necrosis. In a few cases the blood was still fluid and was dark red at the time of the necropsy. One case of sixty-two hours' duration showed 200 c.c. of purulent exudate in the abdominal cavity. In this case there was considerable involvement of the stomach with inflammatory changes reaching to the serosa. In one case death was apparently due to diffuse bronchopneumonia. In a few others, there was a terminal pulmonary edema. In one case the changes were practically limited to the respiratory tract as far as the bifurcation of the trachea.

CHANGES IN THE HEART RHYTHM ASSOCIATED WITH CHEYNE-STOKES RESPIRATION

DISPLACEMENT OF PACEMAKER TO BRANCHES OF BUNDLE OF HIS *

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AND
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The influence of respiration and of vagal stimulation on the location of the cardiac pacemaker and on the form of the ventricular electrocardiogram has been reviewed by Wilson,[1] and need not be detailed here. In brief, so far as man is concerned, the pacemaker may be displaced from its normal location at the sino-auricular node to the auriculo-ventricular node, and vagal stimulation may affect the form of the ventricular electrocardiogram by producing a bundle branch block. In the case described below, marked alterations in the cardiac mechanism were associated with Cheyne-Stokes respiration and were brought about by vagal stimulation. In this instance, changes in the form of the ventricular complexes were due to displacement of the pacemaker into the branches of the His bundle, and it is the purpose of this paper to report such a disturbance in the cardiac mechanism.

REPORT OF CASE

The patient, a colored man, aged 43, entered the hospital, Aug. 4, 1924. His complaint was "shortness of breath and swelling of the legs." About three months before his admission, he began to suffer with dyspnea on exertion, cough, nausea, epigastric discomfort, and edema of the ankles and legs. These symptoms increased in severity, and he was obliged shortly to leave his work.

On physical examination, he presented the usual signs of severe myocardial failure. His heart was enlarged, and there were typical signs of dilatation of the aorta and aortic insufficiency. The blood Wassermann reaction was positive. The respiration was labored and Cheyne-Stokes in character, with periods of apnea of from twenty to twenty-five seconds' duration. At the end of a period of apnea, the heart rate slowed rapidly but not abruptly, to a rate considerably below that present during the period of dyspnea. About fifteen to twenty seconds after the onset of respiration, the heart rate began to increase and, within about twenty seconds, was again equal to that observed during the preceding period of dyspnea. No improvement took place with the usual forms of therapy, including digitalis administration. After the development of a cerebral vascular accident and a resultant hemiplegia, he was transferred, August 28, to another hospital, where he died a month later. Permission for necropsy was not obtained.

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* From the Cardiographic Laboratory of the Johns Hopkins Hospital and University Medical Department.

1. Wilson, F. N.: Arch. Int. Med. **16**:86 (July) 1915; ibid., **16**:1008 (Dec.) 1915.

The relation between the changes in cardiac mechanism and respiration is shown in a semidiagrammatic chart (Fig. 1), based on a continuous record of the heart and respiration taken during an entire apneic and part of the following dyspneic period.

It may be stated at once that the various changes in cardiac mechanism described below were dependent on vagal stimulation. Suitable doses of atropin caused their complete disappearance.

Arterial Blood Gases.—The peculiar and constant relationship of the onset of vagal stimulation to the end of the apneic and beginning of the dyspneic phases of respiration, and its persistence up to the height of the dyspneic period, suggested that the increase in vagal tone was brought on by the same factors that initiated respiration. Before the electrocardiographic curves are described, it may be of some interest to examine

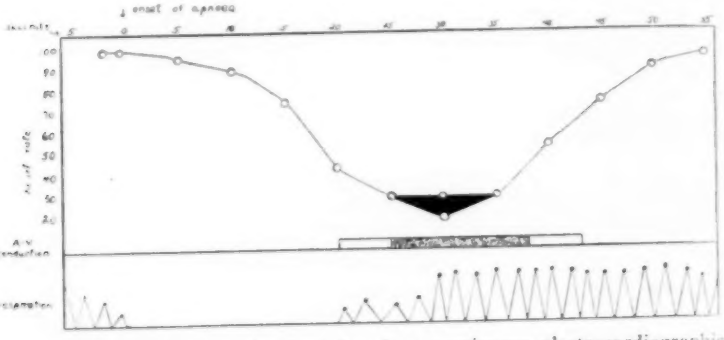

Fig. 1.—Semidiagrammatic chart based on continuous electrocardiographic record on which respiration was recorded. Upper curve: heart rate, accurate except at the lowest rates. Since these occurred during a relatively short period of time, any changes that occurred would be greatly exaggerated if calculations were made for the rate per minute. The shaded area shows the difference between ventricular and auricular rates, the ventricular rate at this time always being greater than the auricular which sometimes averaged only 4-8 beats per minute. Middle line: condition of auriculoventricular conduction, the straight line being the normal, the lightly stippled area representing slight block, and the heavily stippled area, more marked or complete block. The exact time at which these changes took place could not be determined, and this diagram is more or less schematic. The lower curve represents the respirations, and is accurately charted from the respiratory curve.

certain data, which, although incomplete, give some information concerning the cause of the periodic increases in vagal tone.

Arterial blood was obtained during both the apneic and dyspneic periods. The needle was inserted in the brachial artery and the collection of blood was started about five seconds before the end of apnea. With the first attempt at inspiration, the patient was requested to continue to hold his breath in expiration for five more seconds until a

satisfactory sample was obtained. The needle was retained in the artery until the height of dyspnea, when he was requested to continue breathing at the same rate and depth until a second sample of blood was procured. The specimens of blood may be considered to represent good averages of the arterial blood at the end of apnea and at the height of dyspnea. The blood was obtained under oil and handled with the usual precautions. It was analyzed in duplicate by the method of Van Slyke and Stadie.[2]

The figures obtained on analysis are shown in the accompanying table.

There was practically complete oxygen saturation during the dyspneic, and a high degree of saturation at the end of the apneic period. Opposite changes took place in the carbon dioxid content which was somewhat lower than the normal. These results confirm those previously obtained by analyses of the alveolar air at different periods of the respiratory cycle in Cheyne-Stokes respiration;[3] during dyspnea, the tension of

Arterial Blood Gases

	End of Apnea (Duration, 20 Seconds)	Middyspnea
Oxygen content	15.78% by volume	16.15% by volume
Oxygen capacity	16.17% by volume	
Oxygen saturation	97%	100%*
Carbon dioxid content	41.06% by volume	38.87% by volume

* This figure is calculated on the basis of the oxygen capacity of the apneic blood. Since the blood during the dyspneic period was undoubtedly more alkaline,[3] the oxygen capacity would have been higher, and the oxygen saturation slightly lower.

oxygen increases, the tension of carbon dioxid decreases; during apnea, reverse changes take place. In addition, it has been found that the hydrogen ion concentration of the blood is higher at the end of apnea than during dyspnea.[4]

According to Haldane,[5] Cheyne-Stokes respiration is always an evidence of oxygen want. As the arterial blood was practically fully saturated in this patient, anoxemia must have been chiefly of the stagnant type, the slight anemia being disregarded. In the absence of analyses of the venous blood, such an assumption is reasonable in view of the fact that the patient was suffering from a severe degree of heart failure.

It has been found [4] that administration of oxygen or carbon dioxid causes the periodicity in Cheyne-Stokes respiration to disappear. In our patient, the addition of carbon dioxid in the presence of a high concen-

2. Van Slyke, D. D., and Stadie, W. C.: J. Biol. Chem. **49**:1 (Nov.) 1921.

3. Hale White, W.; Ryffel, J. H.; Poulton, E. P.; Johnson, W., and Chisholm, R. A.: Quart. J. Med. **7**:389, 1913-1914.

4. Hale White et al. (Footnote 3). Pembrey, M. S.: J. Path. & Bacteriol. **12**:258, 1908.

5. Haldane, J. S.: Brit. M. J. **1**:409 (March) 1921.

tration of oxygen had such an effect.[6] As the increased concentration of oxygen in the inspired air could have had no appreciable effect in raising the arterial oxygen content, the disappearance of Cheyne-Stokes breathing was due to the increased stimulus to respiration brought about by elevation of carbon dioxid tension of the arterial blood.

Since the administration of carbon dioxid caused the disappearance of the periodic increases of vagal tone, it seems probable that the occurrence of this phenomenon at the end of the apneic period was not due to the increased carbon dioxid tension and hydrogen ion concentration of the blood over that prevailing during the dyspneic period. It appears more likely that the slight lowering of arterial oxygen saturation added to the already marked stagnant anoxemia produced a final anoxemia

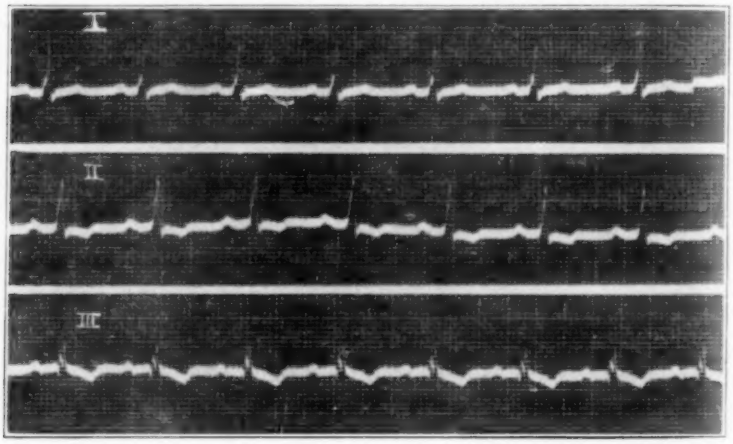

Fig. 2.—Normal and more rapid rhythm. In this and subsequent figures, the heavy time lines represent 0.2 second.

of sufficient severity to stimulate the cardio-inhibitory center.[7] That the heightened vagal tone persisted and increased during the early part of the dyspneic period is ascribed to the shallow and consequently ineffective respirations at this time.

6. Actually, we attempted to administer oxygen without increasing the carbon dioxid content of the inspired gas. This was done before we knew the figures of the blood gas analyses. When it was learned that the dyspneic blood was practically fully saturated with oxygen and that oxygen administration could have had no significant effect in increasing the oxygen content of the arterial blood, we were led to examine the apparatus used for oxygen administration and found that its soda-lime was not effective in completely absorbing carbon dioxid; that is, the patient had been subjected to increasing tensions of carbon dioxid. Owing to the critical condition of the patient, we were unable to make any further respiratory studies.

7. Greene, C. W., and Gilbert, N. C.: Am. J. Physiol. **60**:155 (March) 1922.

DESCRIPTION OF ELECTROCARDIOGRAPHIC CURVES

In Figure 2 are shown the electrocardiograms taken during the normal and more rapid rhythm. The rate was 100 or slightly less; the P-R and Q-R-S intervals were 0.20 and 0.08 second, respectively; the R waves were notched; the T waves were negative in Leads II and III. We shall refer to the type of complexes represented in this curve as the normal for the individual.

Displacement of Pacemaker to Bundle Branch.—Figure 3 (Lead II), taken on August 6, after the patient had received 0.8 gm. of powdered digitalis leaf, illustrates the last three cycles of the rhythm prevailing during the period of slow heart action and the resumption of the normal rhythm. The R-R intervals of the three cycles are 2.25 and 2.22 seconds, respectively. No P waves can be seen to precede the ventricular complexes, which are of abnormal form. Following the T wave of the second cycle there is a small wave of auricular origin to which there is no ventricular response. The T wave of the third ventricular cycle is deformed by another P wave, which is followed after 0.36 second by

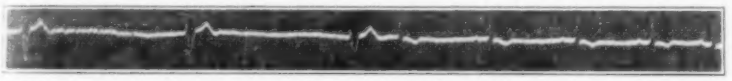

Fig. 3.—Lead II, showing termination of abnormal rhythm and onset of normal rhythm. No P waves precede the first three ventricular cycles, which are of abnormal form. Shortly after the second T wave and superimposed on the third T wave are the outlines of auricular waves.

a normal ventricular complex. This is succeeded by the restoration of the normal rhythm and a gradual increase in heart rate.

The gradual change in rate before the onset of the new rhythm (shown in other figures) and its slow rate show that it is of the so-called homogenetic type. There are two possible interpretations of this rhythm: (1) The impulse may have originated in the His bundle and have traversed one branch due to a blocking of the other; (2) the impulse may have arisen in one of the bundle branches of the ventricular conduction system.

Figure 4 (Lead II), taken on the same day, shows the changes in cardiac mechanism occurring at the end of the apneic and the beginning of the dyspneic phases of respiration. The heart rate, which six seconds previously had been about 85, is slowing rapidly. The first three cycles are of normal form. The third is followed after an interventricular interval of 2.04 seconds by a ventricular complex similar in form to those present at the beginning of Figure 3, and it is reasonable to assume that its origin is the same. It is preceded by an auricular wave of normal form which has no relationship to it, since the distinctly shortened P-R interval indicates that the auricular impulse arising at the sino-auricular

node has reached the ventricle after it had entered into activity. The fifth ventricular beat is an extrasystole. The sixth and seventh ventricular cycles (the last and first of the upper middle curves, respectively) are of normal form, and occur in response to supraventricular stimuli. The eighth ventricular cycle takes place after an interventricular interval of 2.30 seconds and its form is similar to the fourth. It is followed by an inverted P wave, and after a P-R interval of 0.21 second there is a normal ventricular complex. The succeeding cycles occur at gradually increasing rates and have a normal form. The relationship of these changes to respiration is well shown by the respiratory curves at the bottom of the records.

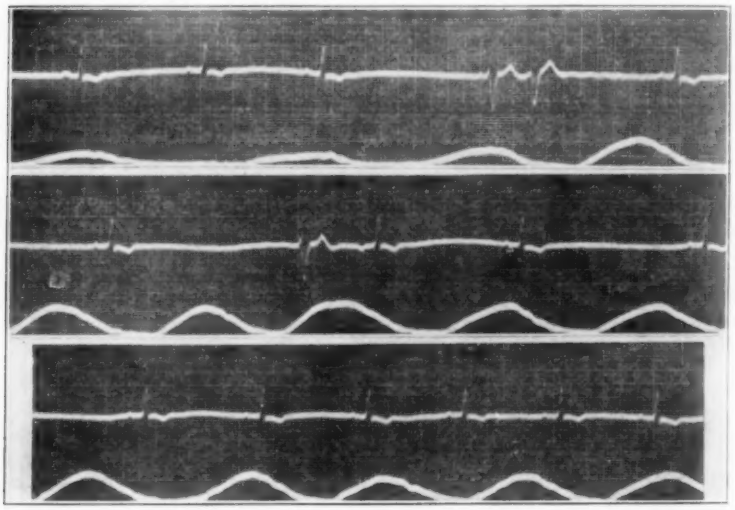

Fig. 4.—Lead II, showing onset of idioventricular rhythm. The curves are continuous, and illustrate the relationship of the changes in rhythm to respiration. The fourth and eighth ventricular complexes are abnormal in form, the sixth and seventh, normal, responding to auricular impulses. The ninth ventricular cycle occurs in response to a stimulus arising in the auriculoventricular node. Following this, the normal rhythm is restored. The curve at the bottom of the record represents respiration, the upstroke being inspiration. The records begin with the onset of the dyspneic period.

These curves demonstrate that, of the two possibilities for the origin of the abnormal rhythm, the second is the correct one; namely, the origin of the ventricular impulse was in one of the branches of the His bundle. When, after the onset of this rhythm, the auricular impulses occur at such a time that the ventricle can respond (Cycles 6 and 7), the form of the ventricular complex is normal. The possibility that a bundle branch block may have existed and disappeared is eliminated by the fact

that when the auricular impulses drop out again, the abnormal type of complex returns (Cycle 8).

Figure 5 (Lead I) is a curve taken, August 7, after the patient had been given 1 gm. of powdered digitalis leaf. The respiration is not recorded, but, as was noted on all previous occasions, the slowing and change in rhythm occurred at the end of a period of apnea. The first two cycles are of normal outline. The third ventricular cycle is not preceded by an auricular wave, and its form is abnormal. A blocked auricular wave follows after an interval of 0.36 second. The next ventricular cycle is similar to the fourth. An auricular wave follows after an interval of 0.52 second, and is responded to after 0.23 second by a normal ventricular complex. The sixth and eighth ventricular cycles are similar in form to the third and fourth, and both are followed by ectopic beats. Between the last two pairs of ventricular beats can be seen the outlines of apparently normal auricular waves. They follow the preceding ventricular cycles at intervals of 0.28 and 0.3 second, respectively. The occurrence of the normal type of ventricular complex in response to the preceding auricular impulse (fifth ventricular cycle)

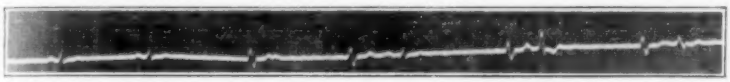

Fig. 5.—Lead I, showing onset of idioventricular rhythm at third cycle. The fifth ventricular complex is normal, responding to an auricular impulse. There are blocked auricular beats after the third, sixth and eighth ventricular cycles. The seventh and ninth ventricular cycles are extrasystoles.

soon after the onset of the abnormal rhythm points even more conclusively to the assumption that the normal form of the ventricular complex in this instance was not merely due to a temporary disappearance of vagal tone. The abnormal rhythm persisted for approximately twenty seconds after its onset, and it is almost certain that vagal tone was increasing rather than decreasing at the time when this ventricular complex was recorded.

For the same reason, the seventh and ninth ventricular beats probably have no relation to the auricular impulses which precede them, since the refractory period of the auriculoventricular node was greater than 0.36 second but a few seconds before at the onset of the heightened vagal tone.

Other records illustrating essentially the same events were procured on different occasions. Although the changes in rhythm were present before digitalis was given, it was found that after effective doses of digitalis, sufficient to produce nausea and vomiting, the abnormal rhythm began to appear earlier in the apneic periods, due undoubtedly to an increase in vagal tone by the drug.

The duration of the pause necessary for the development of the abnormal rhythm varied on different days. Thus, the intervals preceding the two idioventricular beats in Figure 4 were 2.04 and 2.30 seconds. In Figure 5, these intervals were 1.48, 1.42, 1.47 and 1.46 seconds. Rarely, the idioventricular rhythm failed to appear even after a pause greater than was usually necessary on that day. For example, in Figure 4, the interval between the eleventh and twelfth cycles, both normal, was 2.23 seconds, whereas the first idioventricular beat occurred after 2.04 seconds. It may be seen, in Figure 5, that the returning cycles of the idioventricular rhythm after disturbance by the normal cycle or the premature ventricular beats were of approximately the same length as the cycles of the idioventricular rhythm (comparison should be made with Figure 7, taken a few minutes later). This has been described before by Hering.[8]

Auriculoventricular Rhythm.—August 11, there was a short period of auriculoventricular rhythm, which began during a period of apnea

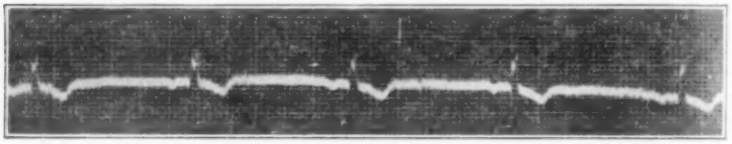

Fig. 6.—Lead III, auriculoventricular rhythm.

and persisted to the middle of the next dyspneic period. This rhythm is illustrated in Figure 6 (Lead III). The inverted P wave and the shortened P-R interval (0.13 second; the normal for the individual is 0.2 second) point to the upper part of the auriculoventricular node as the site of origin of the rhythm.

Auriculoventricular Block.—The changes in cardiac mechanism described above were associated with auriculoventricular heart block (Fig. 1). In general, it was found that, with the development of the abnormal rhythm, the P-R interval of a normal interrupting cycle was increased. With the continuation of the idioventricular rhythm, auricular beats were blocked sometimes after a long ventricular pause, apparently adequate for recovery of the auriculoventricular node. The degree of auriculoventricular block diminished just before the restoration of the normal rhythm.

In Figure 5 there is a blocked auricular impulse occurring 0.36 second after the onset of the third ventricular cycle; 0.52 second after

8. Hering, H. E., cited by Lewis, T.: The Mechanism and Graphic Registration of the Heart Beat, London, 1920.

the next ventricular cycle there is an auricular wave which is followed by a normal ventricular complex after a P-R interval of 0.23 second, the usual P-R interval for this subject being 0.20 second. Figure 7 (Lead I) is a continuation of a record in which the idioventricular rhythm had been present for about fifteen seconds. In the upper part of the curve are six cycles of the idioventricular rhythm. No definite P waves are seen. Thirty-two hundredths second before the seventh ventricular cycle (the first of the lower record which is a direct continuation of the upper) and 1.16 seconds after the sixth ventricular cycle (the last of the upper curve), there is a normal auricular wave. Since the ventricular cycle following the auricular wave is exactly similar in outline to the other ventricular complexes of the same rhythm, one may conclude that it bore no relation to the auricular impulse, and that there was present a complete auriculoventricular block, since, after a long period of recovery, the ventricle failed to respond to the auricular impulse. Because of the movement of the patient, it is difficult to deter-

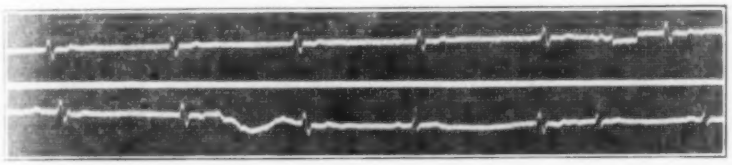

Fig. 7.—Lead I, showing idioventricular rhythm which had been present for fifteen seconds. The upper and lower curves are continuous. Between the sixth and seventh ventricular cycles (the last of upper curve and first of lower) there is a blocked auricular complex, occurring 1.16 seconds after the sixth complex. The tenth ventricular complex is normal, responding to an auricular impulse; the preceding R-R interval is 1.36 seconds. The next ventricular cycle is idioventricular in origin, the preceding R-R interval being 1.52 seconds. The twelfth and thirteenth ventricular cycles (the last two of the lower curve) are normal, and are the first two of the restored normal rhythm. The P-R interval of the twelfth cycle is 0.32 second, of the thirteenth 0.2 second.

mine whether or not an auricular beat occurs between the eighth and ninth ventricular cycles. The next auricular beat is followed by a supraventricular complex after a P-R interval of 0.22 second. Four-tenths second after the eleventh ventricular cycle there is another auricular wave, and, owing to the short period of recovery, the ventricle responds after an interval of 0.32 second. The P-R interval of the next (and the succeeding cycles of the restored normal rhythm) is 0.20 second, normal for this subject. In Figure 4, the ninth ventricular complex occurs in response to an inverted P wave after a P-R interval of 0.21 second. The form of the P wave points to the auriculoventricular node as the site of origin of the stimulus for this cycle. Since the P-R interval was increased over the normal interval of 0.20 second,

that is, vagal stimulation caused a forward block, the impulse must have arisen in the upper portion of the node.[9]

Auricular Standstill.—When the idioventricular rhythm persisted for from twenty to twenty-five seconds, impulse formation in the auricle was frequently inhibited to such an extent that only one auricular wave was seen in a period of about fifteen seconds.

Comment on Changes in Rhythm.—The changes in cardiac mechanism due to vagal stimulation that we have described above are consistent with previous observations, experimental and clinical. In this patient, the important effect of vagal stimulation was to produce displacement of the pacemaker to the branches of the His bundle, auriculoventricular block of varying degree, auriculoventricular rhythm, and marked slowing of impulse formation at the sino-auricular node. Experimentally, the development of heart block and of auriculoventricular rhythm, and the displacement of the pacemaker into one of the branches of the ventricular conduction system, have been described as a result of vagal stimulation.[10] In man, heart block due to vagal stimulation is well known. Wilson [1] has reported the appearance of auriculoventricular rhythm during deep respirations. So far as we can determine, no other instance in man has been described in which the pacemaker has been displaced to one of the divisions of the His bundle by vagal stimulation.

Often the idioventricular beat was followed after a short interval, usually 0.22 to 0.28 second, by an auricular wave. Such an occurrence is illustrated in Figure 5. The auricular waves were always of normal outline, indicating that their origin was in the sino-auricular node. The fairly frequent association of the idioventricular beat followed by an auricular contraction of normal origin permits the suggestion, previously made by Wilson and Robinson,[11] that the contraction of the ventricle may have stimulated the normal pacemaker mechanically.

SUMMARY AND CONCLUSIONS

In a patient with Cheyne-Stokes respiration, marked changes in cardiac mechanism occurred at the end of the apneic and the beginning of the dyspneic periods. These changes were: displacement of the pacemaker to the auriculoventricular node and the bundle branches of the main stem of the conduction system; depression of auriculoventricular conduction, and conspicuous slowing of impulse formation at the sino-auricular node. These changes were due to vagal stimulation.

9. Lewis, T.: Heart **5**:247, 1913-1914.
10. Wilson (Footnote 1, second reference). Cohn, A. E.: J. Exper. Med. **18**:715, 1913.
11. Wilson, F. N., and Robinson, G. C.: Heart Block, Arch. Int. Med. **21**: 166 (Jan.) 1918.

THE OUTPUT OF THE HEART PER BEAT IN HEART DISEASE *

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Heart failure, generally, has been recognized to result in slowing the circulation of the blood. The volume of blood passing through the body at any moment is numerically represented by the product of the pulse rate and the output per heart beat. Since the pulse rate is generally increased in cases of heart failure, it appears reasonable to infer that the slowing of the circulation is due to a greater relative decrease in the output per beat.

The output of the heart per minute in man has been measured by numerous workers.[1] In normal subjects, it has been found to vary between 3.8 and 6 liters. Thus, Lowey and von Schrotters (1903) give 4.2 liters; Plesch (1909), 3.1-5.3; Markoff, Muller and Zuntz (1912), 4-6; Muller (1913), 4.5-5.5; Bornstein (1913), 5-6; Christianson, Douglas and Haldane (1914), 4; Means and Newburgh (1915), 4-4.5; Lundsgaard (1916), male 5.3, female 3.8, and Meakins, Dautrebande and Fetter (1923), male 6.5-8 and female 5.5-7 liters. Lundsgaard [2] found a marked decrease in the volume output of hearts in disease as compared with those of normal persons.

Usually one of two methods, or modifications of them with no essential change in the underlying principles, is employed in determining the output of blood per unit of time in man. One method is based on measurement of the amount of nitrous oxid taken up in unit time from a mixture of nitrous oxid and air with which the lungs are filled. The other consists of simultaneous determinations of the oxygen contents of arterial and venous blood, and the rate of oxygen absorption in the lungs.

In calculations based on data in which the latter procedure is employed, it is generally assumed that the arterial blood is saturated, or nearly so (95 per cent.). Though this assumption may be approximately correct in many instances other than heart disease, in the latter this does not always hold true. It is generally recognized that during heart failure, owing to passive congestion of the lungs, there may be a marked impairment in the efficiency of the latter to aerate completely the blood

* From the Department of Metabolism, Montreal General Hospital.

* This work was done with the technical assistance of Miss Kathleen Wylde.

1. Lundsgaard, C.: J. Exper. Med. **27**:129 (Jan.) 1918; Deutsch. Arch. f. klin. Med. **118**:361, 1916. Henderson, Y.: Physiol. Rev. **3**:165 (April) 1923.

2. Lundsgaard, C.: Untersuchungen über das minuten volume des Herzens bei Menschen, Deutsch. Arch. f. klin. Med. **118**:513, 1916.

passing through. Usually, also, calculations for the venous oxygen are obtained indirectly, i. e., from the use of dissociation curves.

With the development of simplified technical procedures within recent years for the direct determination of the oxygen consumption by the tissues and the oxygen content of arterial and venous blood, no such assumption or indirect calculations are necessary. I have, therefore, attempted to determine the clinical utility of such procedure.

The object of this communication is to record the results that have been obtained in an effort to determine the values for the output of the heart per beat by a combined study of arterial and venous oxygen content and respiratory air analyses with laboratory methods presently available.

CRITICISM OF METHOD

Since variations in the oxygen content of the blood from an arm vein might be caused by factors other than the output of the heart per beat, the chief objection that may be made to conclusions drawn from such observations is that the blood is obtained from a single region (arm) and is assumed to represent the average of that found from the whole body. It is known that there are many factors that influence the oxygen content of arm vein blood. These have been previously discussed by Lundsgaard.[3] This author has aptly suggested comparison of findings with clinical observations and postponement of the conclusions until sufficient data has been accumulated. A few observations appear necessary here and will be made briefly. The fact that the oxygen content of venous blood obtained from an arm differs from that entering the pulmonary artery appears to be admitted by Barcroft and Nagahaski (1921), Peters, Baar and Rule (1921), Uyeno and Doi (1922), Meakins et al. (1922 and 1923) and Stewart (1923). More recently Abbott and Dawson[4] rather strongly emphasized the unreliability of accepting venous blood values so obtained. These authors state, "We cannot find the oxygen content of venous blood by using arm vein blood; with changes of temperature in arm environment, this blood varies all the way from nearly completely reduced to nearly arterial in composition," and quote the observations of Meakins and Davies to substantiate their view.

It is thus obvious that from a consideration of the foregoing observations alone, the method employed here for the estimation of the circulation rate would yield results of doubtful clinical value. One fact needs to be mentioned here, the significance of which will be pointed out later. The oxygen content of blood taken from an arm vein may not be the same as the oxygen content of the mixed venous blood entering the

3. Lundsgaard, C.: Studies of Oxygen in Venous Blood, J. Exper. Med. **27**:179 (Feb.) 1918.

4. Abbott, M. E., and Dawson, W. T.: Internat. Clinics **4**:155 (Dec.) 1924.

pulmonary artery. But, when taken under a uniform set of conditions in health, it appears to have a fairly constant composition. For example, the oxygen unsaturation, when determined by the prescribed method, has been found to vary in persons with no heart failure within narrow limits (Table 1).

This is an important observation since because of this phenomenon values for the circulation may be deduced. It is suggested that when the test is performed under the uniform set of conditions described, the value of the found circulation rate bears the same relation to the true circulation rate as the oxygen content of venous arm blood bears to the oxygen content of the mixed venous blood entering the lungs. That is, it is possible to obtain a relative measure of the circulation rate. Judging from the literature, it appears that by all other procedures values of only such nature are obtained. This may be attributed chiefly to two causes, namely, variations due to (a) uncontrollable physiologic phenomena and (b) technical difficulties.

TABLE 1.—*Oxygen Unsaturation in Persons With no Heart Failure*

	Venous Oxygen Unsaturation
12 normal persons (Lundsgaard)	2.5 to 9 c.c.
12 patients with compensated heart lesions (Lundsgaard)	2.5 to 8 c.c.
40 observations on 4 patients with compensated heart lesions (Lundsgaard)	1.5 to 5.6 c.c.
55 observations on patients with anemia (Lundsgaard)	2.5 to 5.5 c.c.
10 normal persons (author's observations)	3.5 to 5.5 c.c.
15 normal persons (Harrop)	2.6 to 8.8 c.c.

In testing the clinical utility of a laboratory procedure, it need hardly be emphasized that a relative measure of a phenomenon has essentially the same practical value as an absolute measure. For example, it is recognized that the methods generally employed for the estimation of blood sugars do not yield absolute but relative values, since they represent not only sugar but total reducing substances. Day to day fluctuations noted in the course of the treatment of a diabetic patient, however, are of definite clinical significance, bearing a relation to total carbohydrate tolerance. Numerous such examples may be cited.

The values recorded here for the circulation rate are, therefore, regarded as relative. In an individual the absolute value for the circulation rate may be expressed as the product of the relative value and a constant. Thus, $R = r \times k$, in which R = actual volume output per beat; r = calculated volume output per beat, and k = constant.

In evaluating the clinical utility of any laboratory test, the clinical picture must be the guide. It will be shown here that by performing the work under a definite set of conditions, there is correlation between the relative values of the circulation rate obtained and the clinical picture. The differences found between the values in normal individuals

and those with heart failure are so marked and consistent that their significance appears suggestive, in spite of the possible disturbing factors referred to above.

TECHNIC

The oxygen content and capacity of the blood were determined by the gasometric method of Van Slyke.[5] The technic for the collection of the venous blood from the arm vein was that followed by Lundsgaard.[6] Arterial blood was obtained from the radial artery following the procedure described by Stadie;[7] that it is a procedure free from danger was first demonstrated by Hürter[8] and since then by Stadie[7] and Harrop.[9]

In order to insure a successful radial puncture, it is essential to follow in detail the technic as described by Stadie:[7]

> An ordinary 20 c.c. all glass Luer syringe is used with a Luer needle 1 to 2 mm. in diameter. The point of the needle is beveled at an angle of about 45 degrees and must be very sharp. To prevent the blood from coming in contact with air, 1 to 2 c.c. of sterile liquid petrolatum is poured into the barrel of the syringe, the plunger is inserted, and the syringe with the attached needle inverted. The plunger is forced upward, and the air in the dead space at the distal end of the syringe and needle is expelled. The excess of liquid petrolatum is then forced out so that only a small amount remains in the needle and in the small dead space. The patient's arm is laid horizontally upon a pillow, the hand is flexed backwards, and the region over the radial artery is sterilized with tincture of iodin. The end of the left index finger of the operator is then sterilized with iodin and, by using this finger in palpation, the best site for the puncture is determined. (Since the position of the artery is determined by palpation, it is advantageous to avoid gloves and use the bare finger.) The skin at the site of the proposed puncture is anesthetized with procain. The syringe and needle are held at an angle of about 45 degrees to the surface, the needle is then pushed through the skin, and, after carefully relocating its position, the needle is entered into the artery. It is essential that the position of the artery should be sharply located and the point of maximum pulsation chosen (usually opposite the radial styloid); then the artery is easily entered, the pressure of the blood stream forces up the plunger so that suction is unnecessary, and within fifteen to sixty seconds from 10 to 20 c.c. of blood can be obtained. The needle is then quickly withdrawn, and, by means of a compress, firm pressure is immediately applied over the artery for 1 to 2 minutes, so as to obliterate it temporarily and prevent extravasation. The wrist is then bandaged with three or four thicknesses of compress to get greater pressure, and at the end of about three or four hours the bandage may be removed. If the artery is missed at the first puncture, and especially if a hematoma begins to form or blood extravasates around the needle, the operator should desist at once.

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5. Van Slyke, D. D.: Gasometric Determination of the Oxygen and Hemoglobin of Blood, J. Biol. Chem. **33**:127 (Jan.) 1918.

6. Lundsgaard, C.: Studies of Oxygen in the Venous Blood, J. Biol. Chem. **33**:133 (Jan.) 1918.

7. Stadie, E. C.: The Oxygen of the Arterial and Venous Blood in Pneumonia and Its Relation to Cyanosis, J. Exper. Med. **30**:215 (Sept.) 1919.

8. Hürter: Deutsch. Arch. f. klin. Med. **108**:1, 1912.

9. Harrop, G. A., Jr.: The Oxygen and Carbon Dioxid Content of Arterial and Venous Blood in Normal Individuals and in Patients with Anemia and Heart Disease, J. Exper. Med. **30**:241, 1918.

The blood thus collected is transferred to a tube 2.5 by 10 cm. in which a layer of petrolatum at least 2 cm. deep has been placed previously (to prevent contact with air) with some potassium oxalate to prevent coagulation. Not all cases are suitable for arterial punctures, especially when repeated punctures are contemplated. Many women and some men have small radial arteries, deeply situated, and hence difficult to puncture. The more rapid and bounding the pulse, the easier the puncture, and cases of pulse rates of 70 or below are difficult. Occasionally, when the artery has been touched with the point of the needle, it becomes pulseless, due, no doubt, to reflex vasoconstriction, but after fifteen to sixty seconds it relaxes and the puncture may be finished.

Following the puncture there is a numbness of the radial side of the hand, but this wears off quickly. About 50 per cent. of the subjects complain of a very slight, dull pain at the wrist lasting about twelve to twenty-four hours, but this is without significance.

I have not met the possible complications, hemorrhage, thrombosis, embolism and aneurysm.

All observations were made in the postabsorptive state and after thirty minutes of complete muscular rest, *with the arm from which the blood was to be withdrawn at absolute rest for the same period of time.* The arterial blood was first obtained, and within a few minutes (from three to five) the venous blood was withdrawn. For the determination of the oxygen consumption, the Benedict-Roth basal metabolism apparatus was used. While the latter was in progress, the complete blood analyses were made.

The determinations essential for this particular study are: (a) oxygen content of arterial blood; (b) oxygen content of venous blood; (c) oxygen requirement (cubic centimeters per minute), and (d) pulse rate.

From these are calculated: (a) the oxygen consumption (that is the difference between arterial and venous oxygen content); (b) total output of blood per minute from the heart, and (c) the output per beat.

The formula for the relative output per beat is

$$T = \frac{100 \times r}{p\ (a - v)}$$

in which

T = the relative output per beat (cubic centimeters)
r = oxygen requirement (cubic centimeters per minute)
a = the arterial oxygen content
v = venous oxygen content
p = pulse rate.

The combined data are recorded in Tables 2 and 3.

The clinical features in the cases of heart failure are, briefly, as follows:

CASE 1.—A man, aged 53. Diagnosis: Chronic myocarditis; slight dyspnea at rest; no cyanosis. Vital capacity, 1.220 liters.

CASE 2.—A man, aged 57. Diagnosis: Chronic myocarditis; auricular fibrillation; hydrothorax; chronic nephritis; semiorthopnea; general cyanosis. Vital capacity, 0.210 liters.

CASE 3.—A man, aged 44. Diagnosis: Malignant endocarditis; acute nephritis; marked, labored breathing in semiorthopneic position. Vital capacity, 0.860 liters.

CASE 4.—A woman, aged 29. Diagnosis: Chronic endocarditis; mitral stenosis; chronic nephritis; general anasarca, semiorthopnea; general cyanosis. Vital capacity, 0.800 liters.

CASE 5.—A man, aged 62. Diagnosis: Chronic myocarditis; chronic nephritis; marked, labored breathing in orthopneic position; marked general cyanosis. Vital capacity, 0.155 liters.

CASE 6.—A man, aged 48. Diagnosis: Chronic myocarditis; dyspnea at rest; no cyanosis. Vital capacity, 0.510 liters.

CASE 7.—A man, aged 57. Diagnosis: Chronic endocarditis; chronic myocarditis; general anasarca; labored breathing in orthopneic position; cyanosis of lips and fingers. Vital capacity, 0.360 liters.

CASE 8.—A man, aged 61. Diagnosis: Chronic endocarditis; mitral stenosis; right hydrothorax; labored breathing in orthopneic position; general cyanosis. Vital capacity, 0.760 liters.

CASE 9.—A girl, aged 16. Diagnosis: Acute rheumatic fever; chronic endocarditis; slight dyspnea at rest; no cyanosis. Vital capacity, 1.120 liters.

CASE 10.—A man, aged 41. Diagnosis: Malignant endocarditis; cardiac hyperthrophy and dilatation; general anasarca; orthopnea; general marked cyanosis. Vital capacity, 0.216 liters.

In Table 2 are recorded the results obtained from ten persons regarded as normal so far as any evidence of heart disease was concerned. These were, however, all hospital patients. The significance of this fact is pointed out under the discussion of the results.

In Table 3 are recorded the results obtained from ten patients with various heart lesions, all associated with heart failure.

COMMENT ON RESULTS

The average relative ventricular output of blood per beat in ten normal persons at rest, and without any clinical signs of heart failure, was found to be 85.3 c.c. The maximum and minimum values noted were respectively 99.5 and 70.1 c.c. This differed strikingly from the results obtained from the cases of heart failure, in which the average output per beat was found to be 27.3 c.c. with a maximum of 46.2 and a minimum of 13.6 c.c. Thus the differences between the results obtained from normal persons and those suffering from heart failure are in themselves evidence of the significance of this data, in spite of the numerous disturbing factors to be considered in obtaining the blood for analysis from one particular region. That the differences must still be somewhat greater than obtained in these cases is obvious from the fact that the subjects, though accepted as normal so far as heart disease was concerned, were all hospital patients.

Because variations in the pulse rate may affect the ultimate result of such calculations, the data was recalculated on the assumption that in the normal persons the pulse rates were 10 points higher, and in the

patients with heart disease the pulse rates were 10 points lower than found. This would obviously result in decreasing the volume of the output per beat in the normal and increasing it in the pathologic cases.

The data so obtained is also recorded in the Tables 2 and 3, and marked differences are still noted between the results of normal and heart disease cases.

TABLE 2.—*Output of Heart in Ten Patients with Heart Lesions*

Oxygen Capacity, C.c.	Arterial Oxygen Content, C.c.	Venous Oxygen Content, C.c.	Oxygen Consumption, C.c.	Arterial Oxygen Unsaturation, C.c.	Saturation Arterial Blood, Per Cent.	Venous Oxygen Unsaturation, C.c.	Cubic Centimeters Oxygen per Minute Requirement (Basal Metabolism)	Pulse	Output Per Minute	Output Per Beat	Output Per Beat with Pulse Plus 10 Points
16.2	15.7	10.7	5.0	0.5	97.0	5.5	257	68	5,140	75.5	65.9
18.2	17.4	14.0	3.4	0.8	95.7	4.2	224	74	6,588	89.0	78.4
15.3	14.9	11.8	3.1	0.4	97.4	3.5	201	80	6,483	81.0	72.0
17.4	16.7	13.0	3.7	0.7	96.0	4.4	257	76	6,916	91.3	80.7
16.8	16.0	12.3	3.7	0.8	95.3	4.5	217	74	5,894	79.2	69.8
15.4	14.5	10.8	3.7	0.9	94.2	4.6	220	68	5,945	87.4	76.4
14.9	14.2	11.0	3.2	0.7	95.4	3.9	241	82	7,531	91.8	81.8
16.9	16.0	13.1	2.9	0.9	94.7	3.8	189	74	6,517	88.0	77.5
15.8	14.8	11.0	3.8	1.0	93.7	4.8	192	72	5,052	70.1	61.6
16.1	15.2	11.7	3.5	0.9	94.5	4.4	244	70	6,971	99.5	87.1
Average					95.3	...	...	..	.....	85.3	75.1

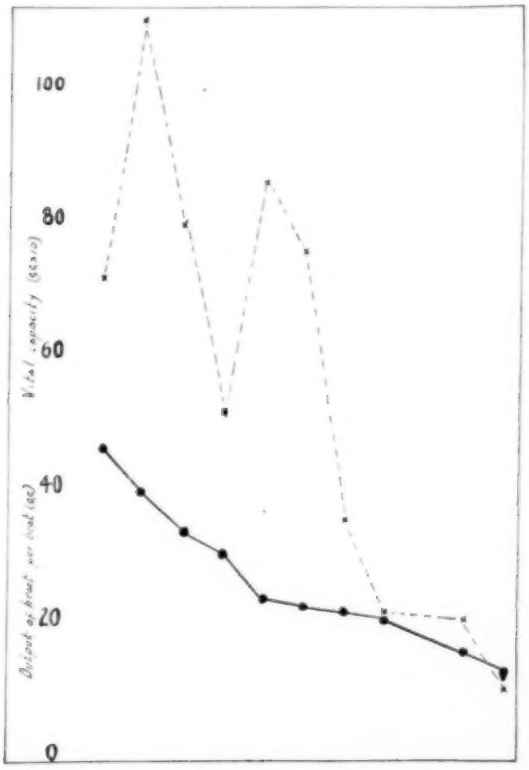
TABLE 3.—*Output of Heart in Ten Patients With Heart Lesions*

Case	Oxygen Capacity, C.c.	Arterial Oxygen Content, C.c.	Venous Oxygen Content, C.c.	Oxygen Consumption, C.c.	Arterial Oxygen Unsaturation, C.c.	Saturation Arterial Blood, Per Cent.	Venous Oxygen Unsaturation, C.c.	Cubic Centimeters Oxygen per Minute Requirement (Basal Metabolism)	Pulse	Output Per Minute	Output Per Beat	Output Per Beat with Pulse Minus 10 Points
1	16.6	14.5	9.1	5.4	2.1	87.5	7.5	210	84	3,868	46.2	52.5
2	19.0	16.3	6.5	9.8	2.7	85.8	12.5	247	116	2,520	21.7	23.7
3	18.0	16.4	6.5	9.9	1.6	91.2	11.5	214	90	2,161	24.0	27.0
4	17.4	15.7	6.9	8.8	2.0	88.8	10.5	264	88	3,030	34.0	38.4
5	16.9	13.5	1.4	12.1	2.4	85.8	15.5	272	128	1,753	13.6	14.8
6	17.4	15.8	8.3	7.5	1.6	90.8	9.1	230	98	3,696	31.2	33.5
7	22.1	18.1	9.2	8.9	4.0	81.9	12.9	244	122	2,741	22.4	24.4
8	21.4	18.0	6.6	11.4	3.1	84.2	14.8	195	72	1,710	23.7	27.5
9	17.7	16.3	9.4	6.9	1.4	92.1	8.3	247	84	3,423	40.5	46.2
10	21.0	18.3	7.7	10.6	2.7	87.2	13.4	214	122	2,018	16.5	18.0
Average						88.5	....	...	...	.....	27.3	30.6

From this data it would be unwise to formulate a definite relation between the output per beat and the clinical picture. Some general agreement was noted in that in Cases 5 and 10, the two apparently more ill patients, the relative values of the output per beat were found to be the lowest, and in two of these cases, Cases 1 and 9, in which there was no appreciable cyanosis and only a very slight dyspnea, the relative values of the output per beat were found to be the highest. There also appeared to be some general agreement in the values for the vital capacity. However, this must be accepted with reserve. The vital

capacity data is recorded in terms of absolute values, since, in the majority of instances, the patients were bedridden and it was not possible to record them in terms of liters per square meter of body surface.

The relation found between the total vital capacity and relative cardiac output is graphically recorded in the accompanying chart. The solid line represents the values for the cardiac output per beat. They are recorded from highest to lowest. The corresponding vital capacity in each is recorded by the broken line.



Relation between total vital capacity and cardiac output.

In all cases of heart failure, with the exception of Cases 1, 6 and 9, there was evidence of cyanosis. An interesting feature is that in these three cases there was little or no evidence of impairment in the pulmonary exchange of gases. In Case 1 there was some impairment in the percussion note at the bases, but the breath sounds were heard. There were a few scattered moist râles. This, however, as Lundsgaard pointed out, is suggestive evidence that the alveoli were patent to air. In

Case 6, there was little impairment in the percussion note at the bases, but the breath sounds were heard. In Case 9, the lungs were normal throughout. When there was no appreciable lung involvement and we were able to exclude the possibility of the slowing of the circulation in the capillaries, due to vasomotor disturbances, it appeared interesting to correlate the degree of arterial oxygen saturation with heart function, i. e., output per beat. The arterial oxygen saturation values in these three cases were, respectively, 87.5, 90.8 and 92.1 per cent., all below the accepted average value for normal subjects, 95 per cent. There is thus suggestive evidence that slowing of the circulation alone may increase the arterial oxygen unsaturation. This applies particularly to Case 9, in which the lungs were found normal throughout.

SUMMARY

1. The relative output of the heart per beat was calculated from the results obtained by the direct determination of the oxygen content of arterial and venous blood in ten normal persons and in ten patients suffering from various heart lesions, associated with heart failure.

2. Marked and consistent differences were noted between the values in the normal and pathologic cases in all instances.

3. There appeared to be some general agreement between the clinical picture and the laboratory data.

4. The technical procedure is practical for clinical purposes and the results are of sufficient interest to warrant further observations along the same lines, especially since at present there is no quantitative method for the estimation of the efficiency of the heart.

DISEASES OF THE LIVER

I. A SURVEY OF TESTS FOR HEPATIC FUNCTION *

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Progress in the science of medicine is dependent on the development of knowledge concerning anatomic and physiologic conditions in health and the disturbances in disease. Each advance, whether in the field of pathologic anatomy or of pathologic physiology, has made possible a better understanding qualitatively and quantitatively of the abnormal process, thus permitting more accurate diagnosis, more exact prognosis, and more rational therapeusis.

As details of the mechanisms controlling normal physiologic activity have come to light, attention has been more directly focused on the changes produced in these mechanisms by disease, and in recent years functional changes have been sought with as great, if not greater, interest than anatomic changes. Exact criteria regarding disturbances of function are not readily delimited. In too many conditions morbid anatomy, valuable as it unquestionably is, has been the only index available to physiologic changes.

Recent improvements in biochemical methods, and consequently in our knowledge of chemical physiology, have been of great practical value, especially in the study of the parenchymatous organs which are the main chemical laboratories of the body. Particularly striking have been the advances in methods of determining changes in renal function. Experience in the comparative study of the different tests proposed has amply demonstrated the relative value of each. Still other tests that will give more accurate or convenient indexes to renal function may yet be devised, but at present many clinicians rely chiefly on the study of the phenolsulphonephthalein excretion and the urea and creatinin content of the blood.

The kidney is preponderantly an excretory organ, and consequently peculiarly suitable for functional study. Both the initial material, the blood, and the excretory product, the urine, are readily available for

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* From the division of medicine, Mayo Clinic and Mayo Foundation and the division of surgery, Mayo Clinic.

analysis. Furthermore, differences in the behavior of the organ toward various materials undoubtedly do exist, but they are differences largely of degree rather than of kind. The functional study of the liver, on the other hand, is much more difficult. Normally, the liver is actively concerned in intermediary metabolism. The formation and excretion of the bile may be, and probably is, an entirely separate and distinct process; also a host of physiologic activities have been ascribed to the liver that may or may not be confined to that organ.

Under such conditions, it is not surprising that a large number of tests have been devised as clinical indexes to functional changes in the liver. Rowntree, Marshall and Chesney [1] in 1914 reviewed the tests in use at that time, and discarded many of them as of little or no clinical value. We have attempted a combined experimental and clinical study of what appears to be the most promising tests in use at the present time, in order to determine their relative clinical value. Many of the previously described tests have been purposely omitted from this discussion. Particular attention has been paid to those furnishing quantitative data in an effort to obtain evidence relating to the degree of hepatic damage. We shall summarize here the theoretical basis, technic and present status of the various tests employed in this work. The results obtained in a series of control cases are shown in the accompanying table. Detailed reports will later be made with regard to the changes observed in a series of 800 cases comprising various pathologic states.

CARBOHYDRATE METABOLISM

The importance of the metabolic activity of the liver, especially in carbohydrate metabolism, was first recognized following the discovery by Claude Bernard of the glycogenic function. Evidences of disturbance in the glycogenic activity of the liver have long been sought. Particular attention has been paid to the study of changes in carbohydrate tolerance, and the earlier studies concerning the relation of the liver to glycosuria have been summarized by Rowntree, Hurwitz and Bloomfield.[2] Of the various sugars, glucose and galactose have proved unsatisfactory in clinical use; fructose has been more satisfactory, but the clinical importance of the fructose tolerance test is still undecided.

1. Rowntree, L. G.; Marshall, E. K., Jr., and Chesney, A. M.: Studies in Liver Function, J. A. M. A. **63**:1533-1537 (Oct. 31) 1914; Studies in Liver Function, Tr. A. Am. Phys. **29**:586-625, 1914.

2. Rowntree, L. G.; Hurwitz, S. H., and Bloomfield, A. L.: An Experimental and Clinical Study of the Value of Phenoltetrachlorphthalein as a Test for Hepatic Function, Bull. Johns Hopkins Hosp. **24**:327-342, 1913; Der Wert des Phenoltetrachlorphthalein für die Funktionsprüfung der Leber, Arch. f. Verdauungskr. **19**:751-753, 1913.

Fructose Tolerance.—It is outside the scope of this paper to attempt to correlate all the facts regarding the absorption, utilization and storage of fructose in the body. The theory, correct or otherwise, on which most observers agree and on which the use of this sugar as a test for hepatic function is founded, is briefly as follows: Fructose is rapidly absorbed from the digestive tract in the normal subject, and is very easily formed into glycogen by the liver. During the whole process, no marked increase in the blood sugar occurs. The rise of the respiratory quotient may be taken to indicate the combustion of a certain part of it. In cases of disease of the liver, glycogen formation supposedly is diminished, and the subsequent rise of blood sugar is assumed to be due in part to fructose that has not been stored or utilized. At least high blood sugar curves after fructose ingestion have been interpreted as due to failure of the glycogenic function of the liver.

Strauss [3] in 1901 investigated hepatic function by an estimation of fructose tolerance. This was suggested by the work of Sachs on hepatectomized frogs. Strauss gave 100 gm. of this sugar and examined the urine by the Seliwanoff reaction. In 90 per cent. of a series of cases of hepatic disease, he obtained fructosuria, which he considered indicative of the inability of the liver to form glycogen from this material, and therefore a measure of hepatic insufficiency. In 10 per cent. of his cases of disease of the liver, negative results were obtained, and in several normals, fructosuria occurred. He explained the negative results by assuming a compensatory hypertrophy of undamaged liver cells, and considered the positive results in normal persons as due to potential or obscure hepatic disorders. Churchman [4] obtained about 24 per cent. of positives in normal persons, and negative results in several patients with malignant disease of the liver. Bloomfield and Hurwitz [5] likewise failed to find the test of clinical value; they objected to it on theoretic grounds, asserting that hypophyseal, pancreatic and neurogenic disorders might alter carbohydrate tolerance; that other organs or even undamaged hepatic tissue might compensate in cases of disease of the liver to give a normal test, and that variations in the renal threshold for fructose must be considered if renal disease was present. Practically, they found that such large doses of sugar caused nausea and vomiting, besides giving

3. Strauss, H.: Zur Funktionsprüfung der Leber, Deutsch. med. Wchnschr. **27**:757-759, 1901. Sachs, Hans: Ueber Bedeutung der Leber für die Verwerthung der verschiedenen Zukerarten im Organismus, Ztschr. f. klin. Med. **38**:87-126, 1899.

4. Churchman, J. W.: The Strauss Test for Hepatic Insufficiency, Bull. Johns Hopkins Hosp. **23**:10-15, 1912.

5. Bloomfield, A. L., and Hurwitz, S. H.: Tests for Hepatic Function; Clinical Use of the Carbohydrates, Bull. Johns Hopkins Hosp. **24**:375-379, 1913.

inconstant clinical results. Folin and Berglund [6] have recently emphasized the importance of impurities in the fructose in producing gastro-intestinal irritation and glycosuria. Friedman [7] concluded that, while fructose tolerance tests might give some information, they could not be interpreted in an absolutely specific manner. Rowntree, Hurwitz and Bloomfield,[2] and Rowntree, Marshall and Chesney [1] in their studies on hepatic function finally discarded the Strauss test as of no clinical value.

With the advent of satisfactory methods for the chemical analysis of the blood, the blood sugar curve, after the administration of carbohydrates, was studied as an index to the carbohydrate tolerance. In 1913, Schirokauer [8] reported blood sugar values one hour after the ingestion of fructose. He found that in the normal subjects only the slightest rise was obtained, in distinction to the sharp increase noted after the taking of a large amount of glucose. In hepatic disease, however, the increase in blood sugar was marked. Bergmark [9] later confirmed this work, and found that fructose caused only the slightest rise in the blood sugar of normal subjects. Isaac [10] asserted that fructose caused no appreciable rise in the blood sugar of normal subjects, although its presence could be demonstrated in the blood, and that in hepatic disease it formed a considerably larger fraction of the total blood sugar.

The present interest in fructose tolerance is largely due to the work of MacLean and de Wesselow.[11] They noted that fructose caused only a slight rise (less than 20 mg.) in the blood sugar of normal subjects, and in 1920 began its use as a test for hepatic function. Using MacLean and de Wesselow's methods, Spence and Brett [12] reported positive results in a variety of hepatic disorders. They gave from 30 to 50 gm. of sugar, and estimated the blood sugar every thirty minutes for two hours; a rise of 20 mg. or more was considered positive. They discarded fructosuria as a criterion of hepatic function, considering that

6. Folin, O., and Berglund, H.: Some New Observations and Interpretations with Reference to Transportation, Retention and Excretion of Carbohydrates, J. Biol. Chem. **51**:213-273 (March) 1922.

7. Friedman, J. C., and Strouse, Solomon: The Nonspecificity of Carbohydrate Tolerance Tests, Arch. Int. Med. **14**:531-535 (Oct.) 1914.

8. Schirokauer, Hans: Zur Funktionsprüfung der Leber, Die alimentärie Lävulose-Hyperglykämie, Ztschr. f. klin. Med. **78**:462-475, 1913.

9. Bergmark, G.: Zuckerresorption und Blutzuckerspiegel, Jahrb. f. Kinderh. **80**:373-385, 1914.

10. Isaac, S.: Theoretisches und Klinisches zur Stellung der Lävulose im Stoffwechsel, Med. Klin. **2**:1207-1210, 1920.

11. MacLean, H., and de Wesselow, O. L. V.: The Estimation of Sugar Tolerance, Quart. J. Med. **14**:103-119 (Jan.) 1921.

12. Spence, J. C., and Brett, P. C.: The Use of Levulose as a Test for Hepatic Inefficiency, Lancet **2**:1362-1366 (Dec. 31) 1921.

the renal threshold for this sugar might show wide variations. Covell[13] in 1923, using the same dosage of fructose and the Folin-Wu technic for estimating blood sugar, obtained positive results in a variety of hepatic disorders, including such tropical diseases as sprue and amebic dysentery. Using the same criterion, he obtained positive results in several cases of amebiasis and assumed that hepatic insufficiency was a common finding. Tallerman,[14] using a dose of from 30 to 50 gm. of fructose in proportion to body weight and MacLean's method of estimating blood sugar, made a careful study of the test; he concluded that variations in normal subjects were greater than generally appreciated, and that unless the height of the curve was 135 mg. per cent. or more, with a maximal rise of at least 30 mg., the finding should be considered negative.

Modern experimental work on animals with these recent modifications of the fructose test has been done by Bodansky.[15] Using 3 gm. of sugar for each kilogram of body weight as a standard dose, he estimated the normal tolerance of dogs for glucose, fructose and galactose. The animals were given the sugar dissolved in 200 c.c. of water by stomach tube, after an initial estimation of their blood sugar when fasting. Blood specimens were then taken after fifteen, forty-five, seventy-five and one hundred thirty-five minutes. Fructose produced the least rise in the curve, galactose the most, glucose occupying an intermediary position. There was no rise greater than 35 mg. in normal animals after the administration of fructose. In dogs who had been under prolonged chloroform anesthesia, a sharp drop in fructose tolerance was found, due presumably to injury of the liver. In other animals, similar changes occurred after intramuscular injections of chloroform in oil. Actual hepatic damage was proved by necropsy. In animals that recovered, the fructose tolerance improved on regeneration of the liver. Similar results were obtained with other hepatic poisons, such as phosphorus and hydrazin and its derivatives.

Method of Determining the Fructose Tolerance.—Patients were given a constant dose of 40 gm. of fructose dissolved in 200 c.c. of lemonade, after an initial blood sugar estimation. All patients had fasted for fourteen hours before the test and took no food until it was completed.

13. Covell, G.: The Levulose Tolerance Test for Hepatic Efficiency, and Its Application in Certain Tropical Diseases, Guy's Hosp. Rep. **73**:354-367, 1923.

14. Tallerman, K. H.: The Levulose Test for Liver Efficiency, and an Investigation of the Hepatic Condition in Pregnancy, Quart. J. Med. **17**:37-52 (Oct.) 1923.

15. Bodansky, M.: Fructose, Glucose, Galactose Tolerance in Dogs, J. Biol. Chem. **56**:387-393 (June) 1923; The Effect of Chloroform and Phosphorus Poisoning on Carbohydrate Tolerance, ibid. **58**:515-522 (Dec.) 1923; The Action of Hydrazin and Some of Its Derivatives in Producing Liver Injury as Measured by the Effect on Levulose Tolerance, ibid. **58**:799-811 (Jan.) 1924.

Blood samples were taken after one and two hours and the blood sugar estimated according to the method of Folin and Wu. The changes in blood sugar in normal persons have been variable, although no greater rise than 30 mg. was noted. We have therefore followed Tallerman,[14] whose criterion for a positive test is a maximal rise of 30 mg. or more, with a one or two hour blood sugar percentage of 135 mg. or more. Detailed reports of our studies in various pathologic conditions will be reported later, but in general we find that the difficulty of excluding extrahepatic influences, especially pancreatic disease, militates against the clinical usefulness of the test as a specific index to changes in the functional activity of the liver.

The Bodansky technic was used for dogs, the animals being given 3 gm. of fructose for each kilogram of body weight, dissolved in from 200 to 300 c.c. of water, by stomach tube. All animals fasted fourteen hours or more. Blood specimens were taken before the sugar was administered and fifteen minutes, one hour and two hours afterward. Accepting Bodansky's criterion, we considered a test positive which showed a rise of 35 mg. or more above the level in the initial specimen. In neither human beings nor dogs was the finding of glycosuria considered significant, in view of the known unreliability of this factor. Because the lesion produced experimentally is much more specific than that observed clinically, a correspondingly greater degree of reliance may be placed on changes in the fructose tolerance.

Blood Sugar Level.—Mann and his associates, in consequence of their experiments on hepatectomized dogs, have further emphasized the rôle of the liver in maintaining the normal blood sugar level. Following operation there is a gradual and progressive fall in the blood sugar; when it decreases below a certain critical level, the body cannot function normally and death occurs. As this critical level is approached a characteristic group of symptoms develop which culminate in the so-called hypoglycemic reaction, first described by Mann [16] and observed clinically in connection with insulin treatment. Hypoglycemia alone can be readily and successfully combated by the administration of glucose, but while this measure will prolong the life of the hepatectomized animal, it must be remembered that total abolition of the normal functional activity of the liver is incompatible with life. Fran and Isaac [17] and, later, Williamson and Mann [18] have shown that hypoglycemia may occur as

16. Mann, F. C., and Magath, T. B.: Studies on the Physiology of the Liver, II, The Effect of the Removal of the Liver on the Blood Sugar Level, Arch. Int. Med. **30**:73-84 (July) 1922.

17. Frank, E., and Isaac, S.: Ueber des Wesen des gestörten Stoffwechsels bei der Phosphorvergiftung, Arch. f. exper. Path u. Pharmakol. **64**:274-292, 1911.

18. Williamson, C. S., and Mann, F. C.: Studies on the Physiology of the Liver, V, The Hepatic Factor in Chloroform and Phosphorus Poisoning, Am. J. Physiol. **65**:267-276 (July) 1923.

a terminal event in phosphorus or chloroform poisoning. Opie and Alford [19] showed the effect of a diet rich in carbohydrates in reducing the toxic action of these poisons. Previous experimental work has indicated that hypoglycemia develops only with practically complete abolition of the glycogenic activity of the liver. Consequently, this condition is not to be expected in the usual types of hepatic disease.

PROTEIN METABOLISM

The importance of the liver in protein metabolism is also recognized, but its exact rôle is not so well understood as it is in carbohydrate metabolism. The topic has been discussed in detail by Van Slyke [20] and Folin and Berglund,[21] and will not be repeated here. Mann [22] has carefully studied changes after ablation of the liver. He finds, as in the earlier studies on animals with Eck fistulas, that there is an increase in the excretion of ammonia and in the proportion of undetermined nitrogen in the urine. In the blood he finds a gradual decrease in the urea, and the rapid appearance of a substance giving the colorimetric reactions of uric acid, of which only traces normally occur in dog's blood. The creatin-creatinin metabolism is not affected. The amino-acids and the nonprotein nitrogen in the blood may be increased slightly, but the changes are much less striking than those in the urea or the uric acid fraction. There have been numerous clinical studies dealing with the nitrogen partition of the urine in patients with hepatic disease, which have arisen from the earlier indentification of leucin and tyrosin crystals in the urine of patients with acute yellow atrophy of the liver. The previous work has been summarized by Rowntree, Marshall and Chesney,[1] and the study of experimental phosphorus and chloroform poisoning by Marshall and Rowntree.[23] These authors report the occurrence of increased ammonia and amino-acids and a decreased urea percentage in the urine. While definite changes were found and are undoubtedly of great significance from the physiologic point of view, the low level of protein metabolism so often present, together with the non-

19. Opie, E. L., and Alford, L. B.: The Influence of Diet upon Necrosis Caused by Hepatic and Renal Poisons, I, Diet and the Hepatic Lesions of Chloroform, Phosphorus or Alcohol, J. Exper. Med. **21**:1-20, 1915.

20. Van Slyke, D. D.: The Present Significance of the Amino-Acids in Physiology and Pathology, Arch. Int. Med. **19**:56-78 (Jan.) 1917.

21. Folin, O., and Berglund, H.: The Retention and Distribution of Amino-Acids with Especial Reference to the Urea Formation, J. Biol. Chem. **51**:395 (April) 1922.

22. Bollman, J. L.; Mann, F. C., and Magath, T. B.: Studies on the Physiology of the Liver, VIII, Effect of Total Removal of the Liver on the Formation of Urea, Am. J. Physiol. **69**:371-392 (July) 1924.

23. Marshall, E. K., Jr., and Rowntree, L. G.: Studies in Liver and Kidney Function in Experimental Phosphorus and Chloroform Poisoning, J. Exper. Med. **22**:333-346, 1915.

exclusion of acidosis, led them to the conclusion that the interpretation of the nitrogen distribution in the urine is somewhat difficult. The inconsistency of results and the further uncertainty regarding renal factors has led us also to question the clinical importance of a study of the nitrogen distribution in the urine as an index to changes in the physiologic activity of the liver.

Attention was later focused entirely on the changes in the blood. Rowntree, Marshall and Chesney [1] apparently were the first to make an extensive study of the nitrogen partition in the blood in its relation to hepatic disturbances. They found no evidence of nitrogen retention except in patients with renal insufficiency. While the changes were not constant, a moderate proportion of their cases showed a lowering in the percentage of the urea. They regarded a low percentage of urea nitrogen as compared to the total nonprotein nitrogen as suggestive of hepatic insufficiency. Our findings have been similar in character, although the changes noted have not been sufficiently well marked to have great diagnostic significance in individual cases.

In contrast to these observations are the experiments of Marshall and Rowntree [23] on the effects of phosphorus and chloroform poisoning. They found an increase in the nitrogenous products of the blood which they interpreted as evidence of an increased protein catabolism. They pointed out that the interpretation of their results was complicated by renal insufficiency which frequently appeared as a terminal phenomenon. Feigl and Luce [24] and Stadie and Van Slyke [25] have reported increases in the nonprotein nitrogen, blood urea, and amino-nitrogen of the blood in patients with acute yellow atrophy of the liver, while Stander [26] has observed similar changes in a fatal case of chloroform poisoning. As pointed out by Greene, Sandiford and Ross,[27] autolytic decomposition of the liver in the latter condition may be largely responsible for the increases noted. Other observers, such as Yanagi,[28] have suggested that the blood urea is decreased in patients with jaundice, while Gilbert,

24. Feigl, J., and Luce, H.: Neue Untersuchungen über akute gelber Leberatrophie, I, Ueber den Restickstoff des Blutes und seine Komponenten, Weitere Beiträge zur vergleichenden Pathologie des Amino-säuresspiegels im Blute, Biochem. Ztschr. **79**:162-201, 1917.

25. Stadie, W. C., and Van Slyke, D. D.: The Effect of Acute Yellow Atrophy on Metabolism and on the Composition of the Liver, Arch. Int. Med. **25**:693-704 (June) 1920.

26. Stander, H. J.: A Chemical Study of a Case of Chloroform Poisoning, Bull. Johns Hopkins Hosp. **35**:46-49 (Feb.) 1924.

27. Greene, C. H.; Sandiford, Kathleen; and Ross, Helen: The Amino-Acid Content of the Blood in Normal and Pathologic Conditions, J. Biol. Chem. **58**:845-857 (Jan.) 1924.

28. Yanagi, K.: A New Colorimetric Method for the Determination of Urea with Urease, J. A. M. A. **82**:1169-1171 (April 12) 1924.

Chabrol and Bénard [29] have reported an increase in the blood urea in patients with hemolytic jaundice.

Mann [30] also has stressed the appearance in the blood of hepatectomized dogs of a substance giving the color reactions of uric acid. This substance appears regularly following removal of the liver, and he considers that in dogs the appearance of uric acid in the blood is very suggestive of decreased activity of the liver. This phenomenon has not been observed in man. The course of purin metabolism differs in man and dog, and it is quite possible that in this field of metabolism especially a direct transference of results from one species to the other should be made with reserve.

BILE PIGMENTS

Since the most striking hepatic disorders are those associated with icterus, it is natural that much attention should have been paid to the presence of bile pigments in the blood, urine and feces. Nature has fortunately provided an excellent index of disturbed pigment metabolism in the color changes in the skin and sclerae, and in the excretion of pigments in the urine and stools. The formation and excretion of bile are characteristic activities of the liver. It is generally accepted that the bile salts are formed by the hepatic epithelium, but it is becoming increasingly apparent that bile pigments may be formed largely outside the liver, although excreted by that organ. Furthermore, as has been repeatedly demonstrated, bile retention rapidly damages the parenchyma of the liver.

A century ago, Tiedemann and Gmelin,[31] in an historically noteworthy book, reported their studies on the physiology of digestion. They described the color changes produced by the oxidation of the bile pigments in acid solution, the series of colors produced by nitric acid still being known as Gmelin's test. By means of this test they demonstrated the presence of bile pigment in the blood of a dog following experimental ligation of the common bile duct, and shortly afterward they successfully applied this test to the serum from a patient with jaundice. It is recognized that, while other allied pigments may occasionally be found in the blood, bilirubin is the only bile pigment present in the serum in appreciable amounts.

Icterus Index.—Various attempts have been made to estimate the bilirubin content of the serum. The simplest methods are based on the assumption that bilirubin is the chief pigment of the serum and, accord-

29. Gilbert, A.; Chabrol, E., and Bénard, H.: L'azotémie dans les ictères par hyperhémolyse, Paris méd. **35**:385-391 (May 8) 1920.

30. Bollman, J. L.; Mann, F. C., and Magath, T. B.: Studies on the Physiology of the Liver, X, Uric Acid Following Total Removal of the Liver, Am. J. Physiol. **72**:629-646 (May) 1925.

31. Tiedemann, F., and Gmelin, L.: Die Verdauung nach Versuchen, Heidelberg and Leipzig, K. Groos, pp. 1826-1827.

ingly, that the intensity of the serum color is an accurate index to the quantity of bilirubin. The serum color has been determined by measuring the number of dilutions necessary to render it just perceptible when viewed in a unit layer of serum, 1 cm. thick. A colorimetric comparison, using a 1 : 10,000 solution of potassium bichromate as a standard, has also been used. The icterus index, based on the latter standard, has been tested clinically by Blankenhorn,[32] Meulengracht,[33] Stetten,[34] Bernheim[35] and others. In general, they found that the values for normal serum are below 5. The threshold for clinical icterus lies between 8 and 15, while marked icterus is present in all cases with values above 30.

The icterus index may be used satisfactorily in following changes in the degree of jaundice in patients with frank icterus. In such patients bilirubin is the preponderate coloring matter, and changes in the serum color may reasonably be assumed to indicate variations in the amount of bile pigment. Conditions are different in specimens of serum in which the bilirubin content is little, if any, increased over the normal. Any cloudiness of the serum or the slightest trace of hemolysis interferes by changing both the quality and intensity of the color of the serum. Van den Bergh and Snapper[36] and Palmer[37] have studied the composition of the serum pigments, and find that serum from human beings contains xanthophyll and carotinoid pigments, which, although varying widely in amount, may be responsible for an appreciable portion of the serum color of the normal. We have observed two patients with pronounced discoloration of the skin and carotinemia after the prolonged use of carrots in their diet. The icterus index in one of the cases was 18, but by chemical methods the serum bilirubin measured only 0.5 mg. per cent., an entirely normal amount. In the second case the icterus index was 26, but the serum bilirubin was only 1.1 mg. per cent.

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32. Blankenhorn, M. A.: Acholuric Jaundice, Arch. Int. Med. **27**:131-134 (Jan.) 1921.

33. Meulengracht, E.: Ein bilirubinkolorimeter behufs klinischer Bestimmung der Bilirubinmenge im Blute, Deutsch. Arch. f. klin. Med. **137**:38 (Aug.) 1921; abstr. J. A. M. A. **77**:1141 (Oct. 1) 1921.

34. Stetten, D.: The Surgical Value of the Estimation of the Bile Pigmentation (Icterus Index) of the Blood Serum, Ann. Surg. **76**:191-200 (Aug.) 1922.

35. Bernheim, Alice R.: The Icterus Index (a Quantitative Estimation of Bilirubinemia): An Aid in Diagnosis and Prognosis, J. A. M. A. **82**:291-295 (Jan. 26) 1924.

36. Van den Bergh, A. A. H., and Snapper, J.: Die Farbstoffe des Blutserums, Deutsch. Arch. f. klin. Med. **110**:540-561, 1913.

37. Palmer, L. S.: Carotinoids and Related Pigments; the Chromolipoids. New York, Chemical Catalogue Company, 1922.

The determination with certainty of changes in the amount of serum bilirubin necessitates the use of a method that will permit of the chemical separation or identification of the pigment. Many methods for the colorimetric determination of bilirubin have been suggested. By modifications in the principle of the original Gmelin test, the attempt has been made to secure green or blue oxidation products of bilirubin under conditions permitting quantitative estimation of the amount of color developed. The details of these various methods have been discussed by Gilbert,[38] Posselt,[39] van den Bergh,[40] Fouchet,[41] and others. None of these methods has been wholly satisfactory, however. The rose colored azobilirubin has been a more satisfactory pigment derivative. The chemistry of the coupling of bilirubin with diazonium salts was investigated by Ehrlich,[42] Pröscher [43] and Orndorff and Teeple.[44] It remained for van den Bergh [45] to apply this reaction to the examination of blood serum, and to develop the test that bears his name.

Van den Bergh Test.—Ehrlich found that when sulphanilic acid and sodium nitrite were added to solutions of bilirubin, a colored addition product, azobilirubin, was formed. This reaction is specific and will detect bilirubin in a dilution of 1 : 1,500,000. Van den Bergh precipitated the serum proteins with alcohol, which also serves as a solvent for bilirubin, and demonstrated that Ehrlich's reaction could be applied to this alcoholic extract. By comparison with solutions of pure bilirubin, a quantitative colorimetric estimation could be made.

Using this method, van den Bergh showed that bilirubin was a constant constituent of normal blood serum, and that the amount was much increased in cases of obstructive jaundice and other hepatic disorders. Later, on investigating the difference in reaction between bilirubin and solutions of human bile, he discovered that the latter gave

38. Gilbert, A.; Herscher, M., and Posternak, S.: Présentation d'un appareil pour doser la bilirubine dans le sérum sanguin (cholémimètre), Compt. rend. Soc. de biol. **51**:700, 1904.

39. Posselt, A.: Zur Methodik der klinischen Serumuntersuchungen Ueber den nachweiskleinster Gallenfarbstoffmengen im Blutserum (Frühdiagnose des Ikterus), Zentralbl. f. inn. Med. **28**:489-509, 1907.

40. Van den Bergh, A. A. H. (with Snapper, J., and Muller, J.): Der Gallenfarbstoff im Blute, Leiden, S. C. Van Doesburgh, **8**:111, 1918.

41. Fouchet, A.: Méthode nouvelle de recherche et de dosage des pigments biliaires dans le sérum sanguin, Compt. rend. Soc. de biol. **80**:826-828, 1917.

42. Ehrlich, Paul: Sulfodiazobenzol, ein Reagens auf Bilirubin, Centralbl. f. klin. Med. **4**:721-723, 1883.

43. Pröscher, F.: Ueber Acetophenonazobilirubin, Ztschr. f. physiol. Chem. **29**:411-415, 1900.

44. Orndorff, W. R., and Teeple, J. E.: On Bilirubin, the Red Coloring Matter of the Bile, Am. Chem. J. **33**:215-250, 1905.

45. Van den Bergh, A. A. H.: La recherche de la bilirubine dans le plasma sanguin par la méthode de la reaction diazoique, Presse méd. **29**:441-443 (June 4) 1921; abstr. J. A. M. A. **77**:235 (July 16) 1921.

positive diazo reactions without the addition of alcohol. From this finding he concluded that there were two types of reaction, one obtained immediately after the addition of the diazo reagent, a "direct reaction," and the other after the addition of the diazo reagent and alcohol, an "indirect reaction." This was explained by the theory that the bilirubin in the bile was somewhat different in composition from the chemically pure substance.

Clinical observations with the van den Bergh reaction have been made by numerous observers (van den Bergh, Lepehne,[46] Rosenthal and Holzer,[47] McNee,[48] Andrewes [49] and others [50]). It is now fully established that normal blood serum may contain from 0.5 to 2 mg. per cent. of bilirubin. Van den Bergh [51] noted that certain apparently healthy persons have somewhat greater amounts of serum bilirubin than others; the former are said to have a physiologic hyperbilirubinemia. Gilbert described the condition, in 1905, as "simple familial cholemia."

In cases of obstructive jaundice, the direct reaction is always present. The amount of serum bilirubin may rise to as much as from 40 to 50 mg. for each hundred cubic centimeters, but the amount of serum bilirubin does not necessarily parallel the discoloration of the skin or the amount of bile pigments in the urine. Mann and Bollman [52] have shown that the van den Bergh reaction becomes indirect, biphasic and then direct in experimental animals following ligation of the common duct. Removal of the gallbladder at the time of ligation of the common duct hastens the onset of the direct reaction. A renal threshold for serum bilirubin in obstructive jaundice has been shown by van den Bergh, Lepehne and McNee.

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46. Lepehne, G.: Weitere Untersuchungen über Gallenfarbstoff im Blutserum des Menschen, Deutsch. Arch. f. klin. Med. **135**:79-107 (Jan.) 1921; abstr. J. A. M. A. **76**:1051-1052 (April 9) 1921; Pathogenese des Ikterus, Ergebn. d. inn. Med. u. Kinderh. **20**:221-280, 1921.

47. Rosenthal, F., and Holzer, P.: Beiträge zur Lehre von den mechanischen und dynamischen Ikterusformen. Ueber die quantitativen Beziehungen von Bilirubin und Cholesterin im Blut bei den verschiedenen Ikterusformen, Deutsch. Arch. f. klin. Med. **135**:257-280 (March) 1921.

48. McNee, J. W.: Jaundice: A Review of Recent Work, Quart. J. Med. **16**:390-420 (July) 1923.

49. Andrewes, C. H.: The Nature of the Difference Between the Bilirubins of Obstructive and Haemolytic Jaundice, Brit. J. Exper. Path. **5**:213-219 (Aug.) 1924.

50. Feigl, J., and Querner, E.: Bilirubinämie in ihren physiologisch-chemischen Beziehungen mit besonderer Berücksichtigung der diagnostischen Bedeutung, Ztschr. f. d. ges. exper. Med. **9**:153, 1919. Andrewes (Footnote 49).

51. Van den Bergh (Footnotes 40 and 45).

52. Mann, F. C., and Bollman, J. L.: The Relation of the Gallbladder to the Development of Jaundice Following Obstruction of the Common Bile Duct, J. Lab. & Clin. Med. **10**:540-543, 1925.

Functional Tests in Control Cases Without Hepatic Disease

Case	Date	Age, Years	Sex*	Edge of Liver Palpable, Cm.	Jaundice †	Urine: Specific Gravity	Urine: Albumin †	Urine: Casts †	Urine: Bile Pigments †	Blood Count: Hemoglobin, per Cent.	Blood Count: Erythrocytes, Millions	Blood Count: Leukocytes	Phenolsulphonephthalein, per Cent.	Blood Nitrogen Partition, Mg., per Cent.: Nonprotein Nitrogen	Urea	Uric Acid	Creatinin	Amino-Acid Nitrogen	Bile Pigments, (Serum): Bile Index	Serum Bilirubin, Mg., per Cent.	Van den Bergh Direct Reaction	Fructose Tolerance, Blood Sugar, Mg., per Cent: Normal	1 Hour	2 Hours	Change	Phenoltetrachlorphthalein: Dye in Serum, per Cent.: 15 Minutes	1 Hour	2 Hours	Dye in Urine, Mg.	Diagnosis
1	6/17/24	29	♀	0	0	1.018	0	0	0	68	3.81	5,800	..	29	26	2.6	1.5	5.1	17	2.0	0	88	107	100	19	9	3	0	0.0	Chronic nervous exhaustion; secondary anemia
2	2/23/24	38	♀	0	0	1.010	0	0	0	78	4.53	8,800	90	..	30	3.2	1.4	...	4	0.3	0	98	100	...	2	9	2	0	0.2	Migraine
3	1/ 7/24	28	♀	0	0	1.028	0	0	0	76	4.55	6,200	50	29	38	...	...	...	..	1.0	0	94	106	100	12	7	2	0	0.0	Functional achylia
4	5/ 2/24	54	♂	0	0	1.029	1	0	0	81	4.80	7,800	..	27	27	2.4	1.7	6.0	6	0.9	0	90	115	83	25	5	2	0	0.0	Psychoneurosis; constipation
5	7/17/24	49	♂	0	0	1.032	0	0	0	80	4.49	6,800	..	29	35	2.9	1.7	6.1	8	1.3	0	..	....	....	..	4	3	0	0.4	Normal
6	2/ 6/24	26	♂	0	0	1.012	0	0	0	75	4.83	7,800	65	..	22	3.3	1.3	...	..	0.5	0	89	106	94	17	4	2	0	0.0	Psychoneurosis
7	1/ 4/24	56	♀	0	0	1.010	1	0	0	76	4.23	6,000	..	27	22	...	...	...	9	0.7	0	100	92	98	—8	4	1	0	0.0	Chronic nervous exhaustion
8	10/10/23	34	♂	0	0	1.020	0	0	0	..	...	.....	..	..	45	...	...	...	..	...	...	..	....	..	..	4	1	0	0.0	Chronic exhaustion
9	11/25/23	51	♂	0	0	1.024	0	0	0	75	...	8,500	60	..	..	...	...	...	..	0.8	0	105	128	104	23	4	0	0	0.0	Normal
10	10/23/23	47	♂	0	0	1.015	0	0	0	76	4.06	7,400	..	..	22	...	...	...	..	...	...	94	100	90	6	3	0	0	0.0	Migraine
11	1/ 3/24	25	♀	0	0	1.027	1	0	0	79	....	9,200	60	26	18	...	...	...	5	0.4	0	70	85	85	15	2	0	0	0.0	Chronic appendicitis
12	9/ 2/24	39	♀	0	0	1.010	0	0	0	80	4.69	9,100	..	26	26	2.4	1.5	5.6	5	0.5	0	84	106	97	22	...	1	0	0.7	Chronic appendicitis
13	9/ 3/24	14	♂	0	0	1.025	0	0	0	..	....	.....	..	..	18	...	2.4	...	..	...	...	..	....	..	..	....	0	0	0.0	Asthma
14	6/ 4/24	26	♂	0	0	1.016	0	0	0	70	4.48	10,300	65	31	21	...	1.7	6.0	7	0.9	0	100	117	116	17	10	3	1	0.3	Chronic infectious arthritis
15	6/ 4/24	47	♂	0	0	1.026	0	0	0	78	4.85	6,900	55	28	27	2.3	1.4	7.1	9	1.4	0	83	110	110	27	5	3	0	0.1	Chronic infectious arthritis
16	6/ 1/23	52	♂	0	0	1.019	0	0	0	77	4.90	16,400	55	..	34	2.8	1.5	5.9	..	...	...	..	..	..	..	6	0	0	0.5	Chronic infectious arthritis
17	1/ 9/24	49	♂	0	0	1.022	0	0	0	82	....	7,800	..	..	26	...	...	...	..	...	..	101	121	111	10	4	2	0	0.0	Chronic infectious arthritis
18	4/29/23	39	♂	0	0	1.041	0	0	0	60	3.76	7,200	55	26	26	1.9	1.4	6.1	5	0.5	0	111	85	108	—26	3	1	0	0.0	Chronic infectious arthritis; secondary anemia
19	11/30/23	40	♀	0	0	1.019	0	0	0	60	4.20	8,500	50	..	21	....	....	....	..	....	....	..	....	....	..	3	1	0	0.0	Chronic infectious arthritis; secondary anemia
20	8/ 7/24	26	♀	0	0	1.019	1	0	0	58	4.20	5,800	60	25	11	2.0	1.1	4.8	..	0.3	0	73	100	...	27	3	1	0	0.2	Chronic infectious arthritis; secondary anemia

* In this table, ♂ indicates male; ♀, female.
† Graded on a basis of 0 to 4.

Although fairly large amounts of serum bilirubin may be present, in cases of hemolytic jaundice it is so masked that the direct reaction is not usually obtained; it is also believed that in this condition serum bilirubin does not pass the renal filter, even when the amount present is considerable. The indirect reaction has aided in the identification of latent jaundice in pernicious anemia, dibothriocephalic anemias and toxic icterus resulting from the administration of arsphenamin. The blood of new-born infants shows an increased serum bilirubin, and in certain instances high figures are said to presage the onset of icterus neonatorum.

In the toxic, catarrhal and infectious types of jaundice, the direct van den Bergh reaction almost invariably occurs, although it may be delayed. The figures for serum bilirubin obtained by the indirect reaction are usually high.

Van den Bergh cites a good deal of evidence derived from experimental and clinical material in support of his view that the direct reaction is a differential point between obstructive and nonobstructive jaundice, and this point has been particularly stressed by his followers, McNee and others. The experiments of Mann, Bollmann and Magath [53] showing the development of icterus in dogs following removal of the liver cast doubt on this view. In such dogs the serum gives first the indirect, then the diphasic, and finally a delayed reaction, which theoretically should not occur in a purely hematogenous icterus such as this. While the exact significance of the direct and indirect reactions is not yet entirely clear and the value of the direct reaction in differential diagnosis is doubtful, enough is known of the indirect reaction as a quantitative measure of the serum bilirubin to assure its accuracy and reliability for clinical purposes. Our study was confined to the amount of bilirubin in the serum indicated by the quantitative indirect reaction. In experimentally produced obstructive jaundice, a very close parallelism exists between the serum bilirubin and phenoltetrachlorphthalein retention, a fact that indicates the close relationship between the degree of icterus and hepatic efficiency.

Method of Determination of Bilirubin.—The quantitative determination of the amount of bilirubin in the blood serum has been made by a modification of the indirect van den Bergh reaction, according to the method of Thannhauser and Anderson,[54] as follows: To 2 c.c. of

53. Bollman, J. L.; Mann, F. C., and Magath, T. B.: Studies on the Physiology of the Liver, IX, The Formation of Bile Pigment After Total Removal of the Liver, Am. J. Physiol. **69**:393-409 (July) 1924.

54. Thannhauser, J. S., and Anderson, E.: Methodik der quantitativen Bilirubinbestimmung im menschlichen Serum, Deutsch. Arch. f. klin. Med. **137**: 179-186 (Aug.) 1921; abstr., J. A. M. A. **77**:1292 (Oct. 15) 1921.

serum is added 1 c.c. of the freshly prepared sulphanilic reagent.[55] The resulting color change permits the reading of the test in terms of the direct or indirect reaction. Then 2 c.c. of a saturated solution of ammonium sulphate is added to help precipitate the serum proteins, followed by 10 c.c. of 96 per cent. ethyl alcohol. This produces a prompt intensification of the color corresponding to the indirect reaction of van den Bergh. The contents of the tube are then centrifugalized and the clear supernatant fluid compared colorimetrically with an ethereal solution of ferric sulphocyanid, prepared according to the directions of van den Bergh.[56] The color quality of the two solutions is not always identical, and other artificial color standards have been advised. In general, however, the foregoing technic has been quite satisfactory.

In their original paper, van den Bergh and Snapper reported their analyses in terms of the dilution of pure bilirubin required to give a solution of the same color concentration as the blood specimen. Later, they [40] reported their results in terms of units, a 1 : 200,000 solution of bilirubin serving as a standard. We have preferred to calculate the results in terms of the number of milligrams of bilirubin for each hundred cubic centimeters of solution, 1 mg. per cent. being equivalent to 2 units. Because of the difficulty of securing pure bilirubin we have accepted van den Bergh's statement that the color of the ferric sulphocyanid standard is equivalent to a 1 : 200,000 solution of bilirubin, or 0.5 mg. per cent. All results obtained by the use of this standard are comparable, and the changes observed are so great that any minor error in the standardization of this solution may be ignored.

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55. This consists of two solutions, each of which keeps indefinitely, but the mixture must be made immediately prior to the test. The two solutions are made up as follows:

Solution A		Solution B	
Sulphanilic acid	5 gm.	Sodium nitrite	0.5 gm.
Concentrated hydrochloric acid	50 c.c.	Distilled water	100 c.c.
Distilled water	1,000 c.c.		

The diazo reagent consists of a mixture of these two solutions in the proportion of 25 c.c. of Solution A to 0.75 c.c. of Solution B.

56. The artificial standard solution (van den Bergh) consists of iron sulphocyanid dissolved in ether. The solution is made up of a color corresponding with a solution of azobilirubin of 1:200,000. The standard solution is made up as follows: 0.1508 gm. of ammonium iron-alum is dissolved in 50 c.c. of concentrated hydrochloric acid, and enough water added to make 100 c.c. This gives a solution of 1:320 normal, which keeps indefinitely. To 10 c.c. of this solution is added 25 c.c. of concentrated hydrochloric acid and sufficient water to make 250 c.c. This gives a dilution of 1:8,000 normal, which keeps for about six months. To 3 c.c. of this solution is added an equal volume of 20 per cent. potassium sulphocyanid solution and 12 c.c. of ether. After being well shaken and after all the reddish color has passed into the ether, the latter is carefully transferred into the colorimeter or other comparative tube. This solution is in a concentration of 1:32,000 normal, and must be prepared freshly each day that a test is made. It corresponds in color, as has been indicated, to a 1: 200,000 solution of azobilirubin, or 0.5 mg. for each 100 c.c.

BILE SALTS

The present day evidence, although incomplete, is all in favor of the view that the bile salts are formed in the hepatic parenchyma. This conclusion is largely the result of studies of the biliary output of these substances, a field recently reviewed and extended in the publications of Whipple and his collaborators.[57]

In the clinical study of hepatic disease, much interest has centered around the possibilities of dissociated jaundice and variations in bile salt metabolism independent of changes in the bile pigments. Much of this work has been based on variations in the surface tension of the urine as shown by Hay's test, which is not specific in nature and does not permit of quantitative study. Foster and Hooper[58] devised an accurate method for the quantitative determination of bile acid excreted in the bile, but this method is not applicable to the smaller amount of bile acids in the urine and blood. Many investigators, among the more recent, Tashiro,[59] have attempted to devise quantitative methods applicable to clinical use, but as no thoroughly satisfactory test has yet been developed, we have not attempted to follow the bile acid metabolism in the present study. Miss Aldrich has recently developed in this laboratory a quantitative method that promises to be applicable to the study of the bile salts in the blood. This will be reported later.

The rôle of bile in the emulsification of ingested fat and the steatorrhea following biliary obstruction are well known. Brulé[60] and others have suggested that bile salts are essential for the absorption of fats from the intestine, and it was on this basis that his hemoconia test was devised. Normally there is an increase in ultramicroscopic blood fat (hemoconia) after a fat meal; this increase does not occur unless bile salts are present in the duodenum. Since stercobilin may appear in the stools when there is complete biliary obstruction, it would seem that this test might be of value in determining the presence or absence of bile salts in the duodenum. In our experience it has given

57. Smyth, F. S., and Whipple, G. H.: Bile Salt Metabolism, I, Influence of Chloroform and Phosphorus on Bile Fistula Dogs, J. Biol. Chem. **59**:623-659 (April) 1924. Whipple, G. H.: Origin and Significance of Constituents of Bile, Physiological Rev. **2**:440-457 (July) 1922.

58. Foster, M. G., and Hooper, C. W.: The Metabolism of Bile Acids, I, A Quantitative Method for Analysis of Bile Acid in Dog's Bile, J. Biol. Chem. **38**:355-366 (June) 1919.

59. Tashiro, S.: Determination of Bile Salts in the Blood (Preliminary Report), Cincinnati J. Med. **4**:197-201, 1923.

60. Brulé, M.: Recherches sur les ictères: les retentions biliaires par insuffisance hépatique, Ed. 3, Paris, Masson et Cie, 1922; Castaigne, J. and Brulé, M.: Foie et pancréas, in: Sergent, E.; Ribadeau-Dumas, L., and Babonneix, L.: Traité de pathologie médicale et de thérapeutique appliqée, Paris, A. Maloine et fils, **12**, 1920.

results comparable with the usual test for bile in the stool, although theoretically it should be somewhat more accurate.

CHANGES IN THE BLOOD ACCOMPANYING DISEASE OF THE LIVER

The frequent occurrence of hemorrhages during the course of hepatic disturbances has long been known. Lee and Vincent [61] more recently have emphasized the close relationship between the tendency toward postoperative hemorrhage in patients with obstructive jaundice and the delay in the coagulation time of the blood. They pointed out that the coagulation of venous blood was greatly retarded, but that the addition in vitro of a calcium chlorid solution greatly accelerated it. Walters [62] has developed the clinical importance of this observation by showing that in such cases the intravenous administration of calcium chlorid will reduce the coagulation time of the blood to within the normal limits of from six to eight minutes. He has shown also that the routine preoperative preparation of jaundiced patients in this way greatly reduces the frequency of postoperative hemorrhages. The beneficial effect of calcium therapy has led to the suggestion that the delayed coagulation in jaundice is due to the absence of available calcium, although it is known that the total calcium content of the serum departs but little, if any, from the normal.

A decrease in fibrinogen was formerly considered a significant finding in suspected hepatic disease, but more recent observations, with improved technical methods, have necessitated a revision of opinion with regard to this point. Whipple and his collaborators [63] have made extensive experimental studies showing the relation of diet, inflammation and other factors to the fibrinogen content of the blood. From their work it would seem difficult to accept variations in fibrinogen as of specific diagnostic value in disease of the liver, as tissue injury in general is an efficient stimulus to increased fibrin production. They conclude, however, that from all available data the liver is the only demonstrable source of fibrinogen in the body.

THE DETOXIFYING ACTIVITY OF THE LIVER

Many toxic substances gain access to the organism only to be rapidly detoxified. By oxidation or conjugation with neutral substances, these

61. Lee, R. I., and White, P. D.: A Clinical Study of the Coagulation Time of Blood, Am. J. M. Sc. **145**:495-503, 1913; Lee, R. I., and Vincent, Beth: The Relation of Calcium to the Delayed Coagulation of Blood in Obstructive Jaundice, Arch. Int. Med. **16**:59-66 (July) 1915.

62. Walters, W.: Preoperative Preparation of Patients with Obstructive Jaundice, Surg., Gynec. & Obst. **33**:651-656 (Dec.) 1921.

63. Foster, D. P., and Whipple, G. H.: Blood Fibrin Studies, IV, Fibrin Values Influenced by Cell Injury, Inflammation, Intoxication, Liver Injury and the Eck Fistula, Am. J. Physiol. **58**:407-431 (Jan.) 1921.

toxic materials are converted into physiologically inert bodies that in turn are excreted through the urine or bile. The oxidation of indol to indoxyl and its ultimate excretion in the urine as indoxyl sulphuric acid; the conjugation of the toxic cholic acid with glycocoll and taurin to form glycocholic and taurocholic acids, which are excreted in the bile, and the formation and excretion of conjugated glycuronates are all evidences of this type of detoxification. The site of this detoxification is not known with certainty, but many of these changes are ascribed to the liver, and consequently there have been many attempts to secure a measure of the detoxifying power of the organism as an index to the functional activity of the liver.

Benzoic acid is detoxified in the organism and excreted as hippuric acid. The liver has been thought to be active in this synthesis, although the kidney apparently is the chief locus of hippuric acid formation. A combined clinical and experimental study of the benzoate test has recently been made by Bryan [64] in this laboratory, and will be reported shortly.

At the time Strauss introduced his fructose tolerance test, he also attempted to measure the detoxifying power of the liver by feeding a known amount of indol and measuring the excretion of indican in the urine. Foster and Kahn [65] fed thymol and measured the increase in the percentage of ethereal sulphates in the urine as an index to the degree of conjugation of the thymol.

Other phenolic substances, including camphor, salicylic acid, cresol, guiacol and menthol have all been used to provoke conjugation. The greatest measure of success with tests of this type has been reported by Roger and Chiray,[66] who gave a provocative dose of camphor and measured the excretion of camphor glycuronic acid. Conjugation was either delayed or diminished in patients with hepatic disorders.

Delprat and Whipple [67] have recently reviewed studies of liver functional tests and reported some of their own experimental studies. More recently Pelkan and Whipple [68] have investigated the appearance of conjugated phenols in the blood following the administration of p-cresol.

64. Bryan, A. W.: Clinical and Experimental Studies on Sodium Benzoate, I. The Value of the Sodium Benzoate Test of Renal Function and the Effect of Injury to the Liver on Hippuric Acid Synthesis, J. Clin. Invest., to be published.

65. Foster, C. S., and Kahn, Max: A Study of the Tests of Liver Function, J. Lab. & Clin. Med. **2**:25-36 (Oct.) 1916.

66. Roger, H., and Chiray, M.: La glycuronurie normale et pathologique; ses variation dans la cirrhose et le diabète, Bull. Acad. de méd. **73**:446-449, 1915.

67. Delprat, G. D., and Whipple, G. H.: Studies of Liver Function, Benzoate Administration and Hippuric Acid Synthesis, J. Biol. Chem. **49**:229-246 (Nov.) 1921.

68. Pelkan, K. F., and Whipple, G. H.: Studies of Liver Function, III, Phenol Conjugation as Influenced by Liver Injury and Insufficiency, J. Biol. Chem. **50**:513-526 (Feb.) 1922.

They found that the conjugation of the phenols in the body was not disturbed by bleeding, by the presence of a biliary fistula, or by a lethal intoxication (distemper). On the other hand, an Eck fistula reduced both the amount and speed of phenol conjugation. Partial exclusion of the liver by ligation of the hepatic artery also reduced conjugation. Slight injury, as a result of chloroform or phosphorus poisoning, was without effect, but extensive injury produced progressively more striking results until, with fatal injury, the phenol conjugation was reduced to zero. These observations led Pelkan and Whipple to the conclusion that phenol conjugation was a function of parenchymal cells of the liver, and of no other body cells. Mann [69] finds, however, that an appreciable degree of phenol conjugation may take place even after complete hepatectomy.

Händel,[70] who studied the excretion of guiacol sulphuric acid and of camphor glycuronate in patients with hepatic disease, did not find constant deviations from normal. Schmid,[71] in a recent report on the camphor test, concludes that it cannot be used as an index to functional changes in the liver, for the locus of conjugation is not known with certainty, the degree of conjugation is not uniform, and it is not possible quantitatively to determine the excretion of glycuronates. In view of the manifest objections we can conclude only that more knowledge concerning the exact mechanism and locus of detoxification in the body is necessary before a study of the conjugating power of the organism can be accepted clinically as an index to the functional activity of the liver.

THE WIDAL HEMOCLASTIC CRISIS

Widal [72] recently has suggested that an important function of the liver is the detoxification of protein-split products, such as proteoses and peptones, formed in the intestinal canal during digestion. Failure of this proteopexic activity of the liver permits the passage of such products into the general circulation where an anaphylactic reaction is produced. This last is evidenced by changes in the blood pressure, but especially by a transitory leukopenia, the hemoclastic crisis.[72] The usual practice is to make a leukocyte count after a fast of at least five hours.

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69. Mann, F. C.: Personal communication to the authors.

70. Händel, M.: Klinisch-experimentelle Studien über die entgiftende Funktion der Leber, I, Ueber Schwefelsäure- und Glukuronsäurepaarung bei Leberkranken, Ztschr. f. d. ges. exper. Med. **42**:172-193, 1924.

71. Schmid, F.: L'épreuve de la fonction hépatique par la glycuronurie provoquée, Ann. de méd. **13**:328-358 (April) 1923.

72. Widal, F.; Abrami, P., and Iancovesco, N.: L'épreuve de l'hémoclasie digestive dans l'étude de l'insuffisance hépatique, Presse méd. **2**:893-898, 1920; Feinblatt, H. M.: Alimentary Leukocytosis in Various Pathologic Conditions: A Further Study in Reference to the Crise hémoclasique of Widal, Arch. Int. Med. **33**:210-216 (Feb.) 1924.

The subject is then given 200 c.c. of milk, and the leukocyte count repeated at half-hour intervals. Normally the usual postalimentary leukocytosis follows, but leukopenia is observed in a variable proportion of subjects in both health and disease. The significance of the test is uncertain and many observers are agreed as to the great variability in the response. We have been unable satisfactorily to correlate the test with other clinical and laboratory evidences of hepatic disturbance, and question its value in the diagnosis of disease of the liver.

PHENOLTETRACHLORPHTHALEIN

Phenoltetrachlorphthalein was first prepared by Orndorff and Black[73] in 1909. Pharmacologic studies by Abel and Rowntree[74] showed that, when given by mouth to healthy animals, the drug was not absorbed from the intestinal tract, but when given parenterally in moderate doses either intravenously or subcutaneously, dissolved in oil, the dye was excreted solely in the bile. The specificity of this path of excretion suggested the use of phenoltetrachlorphthalein as a test for hepatic function.

This test, as originally described by Rowntree, Hurwitz and Bloomfield, was carried out by the intravenous injection of a solution containing 400 mg. of the dye. Active purgation was instituted and the total feces were collected for a period of forty-eight hours. The total amount of dye in the specimen of stool was then determined. In a series of normal patients, from 30 to 50 per cent. of the dye injected was recovered in the stools. From patients with disease of the liver the proportion of dye recovered was significantly decreased.

Whipple, Peightal and Clark[75] studied the output of phenoltetrachlorphthalein in experimental animals, and found that the degree of hepatic damage produced in dogs by chloroform or phosphorus poisoning or cautery of the liver was paralleled by the drop in the excretion of the dye.

Subsequent opinions regarding the original test have varied greatly. Rowntree, Marshall and Chesney,[1] in 1915, reported another series of cases, extending and amplifying the original report. Krumbhaar[76] likewise considered the test of definite value. On the other hand,

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73. Orndorff, W. R., and Black, J. A.: Phenoltetrachlorphthalein and Some of Its Derivatives, Am. Chem. J. **41**:349-393, 1909; Chem. Abst. **3**:1875-1876, 1909.

74. Abel, J. J., and Rowntree, L. G.: On the Pharmacological Action of Some Phthaleins and Their Derivatives, with Especial Reference to Their Behavior as Purgatives, I, J. Pharm. & Exper. Therap. **1**:231-264, 1909.

75. Whipple, G. H.; Peightal, T. C., and Clark, A. H.: Tests for Hepatic Function and Disease Under Experimental Conditions: Phenoltetrachlorphthalein, Bull. Johns Hopkins Hosp. **24**:343-357, 1913.

76. Krumbhaar, E. B.: The Present Status of Functional Liver Tests, New York M. J. **100**:719-721, 1914.

Sisson,[77] McLester and Frazier[78] and Kahn and Johnston,[79] who reported smaller series of cases, were doubtful of the value of the test.

The original technic of Rowntree, Hurwitz and Bloomfield[2] was time consuming and the collection and analysis of the specimens of stools unpleasant and difficult. These objections led McNeil,[80] in 1915, to abandon entirely the collection of stools. He substituted for it the passage of a duodenal tube, and the determination of both the time interval elapsing between the injection of the dye and its appearance in the duodenal drip, and the amount of dye recovered during a two-hour period of drainage. McNeil, and Piersol and Bockus[81] report that the time of the appearance and the total output of the dye are related. Deakin and Graham[82] maintained that the uncertainty regarding the quantitative recovery of bile through the duodenal tube militated against any study of the total output of phenoltetrachlorphthalein, and this view is now widely accepted. The normal time of appearance of the dye in the duodenal drip varies between fifteen and twenty-five minutes. Numerous observers, including Kahn,[83] Aaron, Beck and Schneider,[84] Williams,[85] Piersol and Bockus,[81] Higgins[86] and Friedenwald and Gantt[87] are agreed that pathologic cases usually show sufficient delay in the time of appearance to make the test of distinct clinical value.

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77. Sisson, W. R.: A Clinical Study of Two Hepatic Functional Tests (Galactose and Phenoltetrachlorphthalein), Arch. Int. Med. **14**:804-826 (Dec.) 1914.

78. McLester, J. S., and Frazier, Blanche: Phenoltetrachlorphthalein Test of Liver Function in a Series of Unselected Cases, J. A. M. A. **65**:383-387 (July 31) 1915.

79. Kahn, M., and Johnston, J. R.: The Phenoltetrachlorphthalein Test of Liver Function, New York M. J. **102**:848-850, 1915.

80. McNeil, H. L.: The Quantitative Estimation of Phenoltetrachlorphthalein Excreted in the Fresh Bile in Disease of the Liver, J. Lab. & Clin. Med. **1**:822-825, 1915.

81. Piersol, G. M., and Bockus, H. L.: The Value of Phenoltetrachlorphthalein in Estimating Liver Function, Tr. A. Am. Phys. **37**:433-451, 1922; Arch. Int. Med. **31**:623-636 (May) 1923; Comparative Studies in Liver Function by Some of the Later Methods, J. A. M. A. **83**:1043-1049 (Oct. 4) 1924.

82. Deakin, V. R., and Graham, E. A.: Functional Liver Tests; an Experimental Study, Surg., Gynec. & Obst. **36**:348-354 (March) 1923.

83. Kahn, Max: Phenoltetrachlorphthalein Estimation in the Duodenal Contents, J. A. M. A. **77**:41 (July 2) 1921.

84. Aaron, A. H.; Beck, E. C., and Schneider, H. C.: The Phenoltetrachlorphthalein Test for Liver Function, J. A. M. A. **77**:1631-1634 (Nov. 19) 1921.

85. Williams, P. F.: The Phenoltetrachlorphthalein Test for Liver Function in Pregnancy. Am. J. Obst. & Gynec. **4**:26-30 (July) 1922.

86. Higgins, C. C.: Observations upon the Phenoltetrachlorphthalein Test for Liver Function, Ann. Clin. Med. **2**:30-18 (July) 1923.

87. Friedenwald, J., and Gantt, W. H.: Some Observations on the Phenoltetrachlorphthalein Test as a Means of Determining Liver Function, Am. J. M. Sc. **166**:519-526 (Oct.) 1923.

Hoxie,[88] on the other hand, does not consider the time of appearance to be sufficiently uniform for routine clinical use. The arguments for and against the study of the appearance of phenoltetrachlorphthalein apply with equal force to the use of other dyes, such as methylene blue or rose bengal, in chromocholoscopy.

The difficulties and impracticability of studying the excretion of phenoltetrachlorphthalein in the stools or duodenal contents were later emphasized by Rosenthal.[89] After the intravenous injection of the dye, he found it to be removed from the blood stream very rapidly and uniformly. In normal persons only from 2 to 7 per cent. of the dye was found in the blood serum fifteen minutes after the injection, and less than 3 per cent. at the end of an hour. Experimental studies by Rosenthal showed that after phosphorus or chloroform poisoning or partial removal of the liver there was a marked retention of the dye in the blood stream. Lamson [90] has also used this method with success in his study of the toxic effects of carbontetrachlorid.

As the result of his experimental studies, Rosenthal suggested the rate of removal of phenoltetrachlorphthalein from the blood stream as the most satisfactory clinical test of hepatic disturbance. Rosenfield and Schneiders,[91] and Greenbaum and Brown [92] have reported small series of cases indicating the value of this test in the toxemias of pregnancy and in syphilitic affections of the liver. In the present study, the rate of removal of this drug from the blood stream was determined according to the principles outlined by Rosenthal. Because of minor variations in the technic used we shall describe our method in detail.

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88. Hoxie, G. H.: Phenoltetrachlorphthalein Liver Function Test, J. A. M. A. **82**:361-362 (Feb. 2) 1924.

89. Rosenthal, S. M.: An Improved Method for Using Phenoltetrachlorphthalein as a Liver Function Test, J. Pharm. & Exper. Therap. **19**:385-391 (June) 1922; A New Method of Testing Liver Function with Phenoltetrachlorphthalein, II, Bull. Johns Hopkins Hosp. **33**:432-437 (Dec.) 1922; A New Method of Testing Liver Function with Phenoltetrachlorphthalein, III, Clinical Report, J. A. M. A. **79**:2151-2154 (Dec. 23) 1922; A New Method of Testing Liver Function with Phenoltetrachlorphthalein, IV, The Relation of Impaired Function to the Amount of Normal Liver Tissue, J. Pharm. & Exper. Therap. **23**:385-393 (June) 1924; Proc. Soc. Exper. Biol. & Med. **21**:73-75, 1923-1924; The Phenoltetrachlorphthalein Test for Hepatic Function, Recent Studies with the Author's Method, J. A. M. A. **83**:1049-1053 (Oct. 4) 1924.

90. Lamson, P. D.; Gardner, G. H.; Gustafson, R. K.; Maire, E. D.; McLean, A. J., and Wells, H. S.: The Pharmacology and Toxicology of Carbon Tetrachlorid, J. Pharm. & Exper. Therap. **22**:215-288 (Nov.) 1923; The Toxicity of Carbon Tetrachlorid in Relation to Liver Function as Tested by Phenoltetrachlorphthalein, J. Pharm. & Exper. Therap. **21**:237-246 (May) 1923.

91. Rosenfield, H. H., and Schneiders, E. F.: Improved Phenoltetrachlorphthalein Test for Liver Function in Pregnancy and Its Toxemias, J. A. M. A. **80**:743-747 (March 17) 1923.

92. Greenbaum, S. S., and Brown, H.: The Phenoltetrachlorphthalein Liver Test, in Cases of Acute and Chronic Syphilis Under Treatment and in Various Skin Diseases, J. A. M. A. **82**:88-91 (Jan. 12) 1924.

Method of Determining Rate of Removal of Phenoltetrachlorphthalein from the Blood Stream.—The phenoltetrachlorphthalein is injected intravenously in a dosage of 5 mg. for each kilogram of body weight. This corresponds to 1 c.c. of the solution prepared according to the original directions of Rowntree, Hurwitz and Bloomfield for each 10 kg. of body weight.[93] If a large superficial vessel in which there is a free flow of blood, such as the median cubital vein, is chosen and the undiluted dye solution is injected slowly enough (from 1 to 2 c.c. each minute) to permit of considerable dilution by the blood stream during the injection, no reaction follows. If the injection is made into one of the other superficial veins, such as the cephalic, in which the blood flow is not so great, or if the injection is made too rapidly, there may be a sensation of a transient burning along the course of the vein. Occasionally slight induration or local thrombosis at the site of injection occurs, especially if the dye solution is allowed to leak back from the vein into the subcutaneous tissues.

The majority of observers who have injected phenoltetrachlorphthalein in amounts similar to those used in this study have diluted the dye with distilled water or salt solution. Such dilution requires the administration of the dye by gravity or the use of some special three-way stopcock to permit the washing out of the system. The simplicity of the apparatus and the resultant ease of sterilization and administration, we believe, commends the direct method of injection. On account of the irritant action of the dye solution, the greatest care and exactitude are required in its administration.

Following the injection of the phenoltetrachlorphthalein solution, blood samples are taken at fifteen minutes, one hour and two hours. These samples are preferably taken from the other arm in order to avoid the possibility of contamination from the retention of dye at the site of injection, although this danger is negligible in practice. We have noticed no difference in the readings of serum and plasma samples provided they are unhemolyzed.

The amount of dye in the serum is most easily determined by dividing the sample between two tubes of equal caliber. A trace of alkali suffices to develop the maximal color of the dye in one tube, while the other serves as a control. Comparison is then made against standard tubes of dye, using the Walpole[94] method of compensating for the serum color. Hemolyzed bloods are precipitated by acetone, as suggested by Bloom

93. Ampules containing a stable solution of phenoltetrachlorphthalein of this concentration are now prepared by Hynson, Westcott & Dunning.

94. Walpole, G. S.: Chart Presentation on Recent Work on Indicators, Biochem. J. **5**:207-214, 1911.

and Rosenau.[95] The extraction of dye by acetone is not entirely complete, but the method is satisfactory for ordinary purposes. We have adhered to Rosenthal's original method [96] of notation in reading the dye in percentage of an assumed initial concentration. Variations in the plasma volume introduce minor inaccuracies in this system of notation, but this error is too slight to be significant and may be disregarded.

The comparison of different patients or of a series of tests on the same patient necessitates a uniform notation of the degree of dye retention indicated by each test. Lamson [90] has introduced the conception of a "toxicity index" based on the total area subtended by the curve showing the concentration of dye in the plasma. The accurate determination of this curve of concentration requires repeated venipuncture up to the time of disappearance of the dye from the plasma, and the use of a planimeter for the measurement of the area subtended by the resultant curve. Lamson has pointed out the difficulties in the use of this toxicity index, and admits that at best the values are approximate only.

We have preferred to refer to positive readings as indicating slight, moderate, marked and maximal degrees of retention. Both the concentration of the dye at the initial reading and the rate of removal from the blood stream are considered in this determination of degree of retention. When a comparison of several readings has been made, we have usually taken the one-hour readings. This is the most valuable single sample, but our knowledge of the test is not as yet sufficient to warrant the entire dependence on this one sample, as suggested by Bogen.[96]

Urinary Excretion of Phenoltetrachlorphthalein.—Rowntree, Hurwitz and Bloomfield mentioned the urinary excretion of phenoltetrachlorphthalein in their original papers. They did not find the dye in the urine of any normal subject, and believed that its appearance in the urine was of distinct clinical significance. Subsequent investigators either have not studied the urinary output, or else have not considered it significant.

As a matter of routine we have collected the urine over a period of two hours following the injection of phenoltetrachlorphthalein. Traces of the dye may appear in the urine of normal subjects, but only in exceptional instances does the total output exceed 0.5 mg. The urinary output apparently is dependent on the concentration of the dye in the blood, and amounts of 1 mg. or more are indicative of definite retention

95. Bloom, W., and Rosenau, W. H.: A Simple Method for the Determination of Phenoltetrachlorphthalein in Blood Serum, J. A. M. A. **82**:547 (Feb. 16) 1924.

96. This method of determining the content of dye has been developed independently by Bogen (A Clinical Test for Liver Function, J. Lab. & Clin. Med. **8**:619-621 [June] 1923), Broun, and Rosenthal. The standard tubes of phenoltetrachlorphthalein fade readily when exposed to light and may well be replaced by the inorganic standard solution developed by Hynson, Westcott & Dunning.

of dye. It must be remembered that the renal excretion is dependent partly on the functional activity of the kidneys, and patients with combined hepatic and renal disease may not show a urinary excretion of phenoltetrachlorphthalein commensurate with the degree of retention in the blood. In doubtful cases, however, the urinary findings may be of distinct clinical value.

BROMSULPHALEIN

Recently, White [97] has prepared a disulphonic derivative of phenoltetrabromphthalein. The disodium salt of this derivative (bromsulphalein [97]) is readily soluble in water, forming a colorless, neutral, nonirritating solution. The addition of an excess of alkali suffices to produce the characteristic reddish violet of the original dye. The physiologic properties of this new derivative apparently are very closely allied to those of the phenoltetrachlorphthalein, but because of the neutral and therefore nonirritating character of the solution, the disulphonic acid derivative may prove of superior usefulness for routine use. The latter dye leaves the blood stream somewhat less rapidly than the original, and accordingly is a more sensitive indicator of small degrees of change.

COMMENT

We have here tried to give an outline of the reported tests for those physiologic changes in the liver which gave sufficient evidence of clinical usefulness to warrant further study. In the subsequent papers of this series, we shall report the results of a comparative study of certain of these tests in various clinical and experimental conditions.

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97. Rosenthal, S. M., and White, E. C.: Studies in Hepatic Function, VI. A, The Pharmacological Behavior of Certain Phthalein Dyes; B, The Value of Selected Phthalein Compounds in the Estimation of Hepatic Function, J. Pharm. & Exper. Therap. **24**:265-288 (Nov.) 1924; Clinical Application of the Bromsulphalein Test for Hepatic Function, J. A. M. A. **84**:1112-1114 (April 11) 1925.

DISEASES OF THE LIVER

II. A COMPARATIVE STUDY OF CERTAIN TESTS FOR HEPATIC FUNCTION IN EXPERIMENTAL OBSTRUCTIVE JAUNDICE *

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Study I of this series was devoted to a consideration of the physiologic basis, technic and interpretation of a number of clinical tests for functional disturbances of the liver.[1] The present study of tests for hepatic function in experimental obstructive jaundice was undertaken with the view of: (1) delimiting the relative value and significance of the various tests under controlled conditions, (2) establishing an experimental background for the better interpretation of the functional deviations clinically observed in patients with obstructive jaundice, and (3) correlating, so far as possible, the physiologic changes indicated by the various tests with the pathologic changes observed at necropsy.

Two groups of six dogs each were studied: those which had had simple ligation of the common duct, and those which had had cholecystectomy besides ligation of the common duct. In all cases complete studies with regard to the tests to be employed were made before the operation, and at intervals of from one to three days during the period immediately following the production of the obstruction. With the development of marked jaundice there were definite changes in the functional tests. Subsequently, the changes were less rapid, and tests were made at weekly intervals. A second operation was performed in a few instances to relieve the obstruction, and the course of the recovery was studied.

The animals were kept on a constant diet of meat, milk and dog biscuit. Following ligation of the common duct, the dogs of the first group manifested but little postoperative reaction and were in good condition for the first three to five days, when icterus became prominent; thereafter they developed lassitude, anorexia, weakness and progressive emaciation. The animals of the second group, in which the gallbladder was removed at the time the common duct was ligated, developed a profound intoxication and icterus within twenty-four hours after operation.

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* From the Division of Medicine, Mayo Clinic and Mayo Foundation.
1. Greene, C. H.; Snell, A. M., and Walters, Waltman: Clinical and Experimental Studies in Diseases of the Liver, I, A Survey of Tests for Hepatic Function, Arch. Int. Med. **36**:248 (Aug.) 1925.

These dogs usually improved somewhat after a few days, and thereafter the clinical condition of the animals of the two series was similar.

Control experiments were made to determine the specific effects of the anemia, acidosis, anorexia and loss of weight incidental to the experimental procedures. A few animals were fed daily by stomach tube a mixture of corn syrup and milk, to prevent the loss of weight following operation. These animals remained in a somewhat better condition than those allowed to eat at random, but the changes in the responses to the different tests were identical in the two series. In further control experiments on normal animals, the effects were studied of fasting that caused a loss of 40 per cent. of the initial body weight; of acidosis produced by a ketogenic diet and the administration of ethyl aceto-acetate, and of anemia produced by either a single large bleeding or several small bleedings. In general the latter procedure had but little effect on the results of the different tests.

DATA IN EXPERIMENTAL JAUNDICE

The functional disturbances observed following the production of obstruction were strikingly uniform in both series of experiments. Five animals in which complete studies were made were included in each series. Slight individual variations occurred, but the results, as examplified by these animals, were quite constant for each experimental series.

PROTOCOLS

EXPERIMENT 1.—Dog H26 was an adult male, black and white mongrel in good condition, weighing 13.4 kg. March 31, a complete series of functional tests was performed. April 1, the phenoltetrachlorphthalein test was repeated as an additional control. April 3, under ether anesthesia and using aseptic technic, the common duct was doubly ligated and sectioned between clamps. The gallbladder was not disturbed. April 4, the animal was in good condition and without evidence of postoperative reaction. The functional studies were repeated (Fig. 1). April 7, slight icterus was apparent in the skin and conjunctiva. There was then a gradual increase in the degree of apparent icterus associated with progressive anorexia and loss of weight. The findings in the different tests are shown in Table 1. May 6, an attempt was made to relieve the obstruction. At operation the cut end of the obstructed common duct was readily found, as it was dilated to many times the normal diameter. An anastomosis was made between the dilated duct and a loop of the ileum. The operation was difficult and there was some unavoidable soiling of the operative field. The animal did not do well and died twenty-eight hours later. Functional studies were made immediately before death.

At necropsy immediately after death, the mucous membranes were jaundiced in appearance and the tissues bile stained, especially the intimal lining of the heart and aorta. Only small amounts of dirty yellow omental fat were observed. There was no free fluid in the peritoneal cavity. The anastomosis was intact, and the intestine contained bile. The extrahepatic bile ducts were greatly dilated, and the thin-walled, distended gallbladder contained thick, viscid green bile. The liver was shrunken, congested and mottled in appearance. The intrahepatic bile ducts were moderately dilated. The mesenteric lymph

nodes were enlarged, and there was an acute pancreatitis with multiple areas of fat necrosis. The spinal fluid and aqueous humor were colorless, and qualitative tests for bile pigments were negative.

Microscopic examination of the liver (Fig. 2) disclosed a slight increase in connective tissue around the bile ducts with beginning round cell infiltration. In the central portion of the lobule there was a slight staining from bile, and a few bile thrombi were present in the canaliculi. The parenchymal cells were swollen, the sinuses compressed, and there was no increase in the endothelial cells.

EXPERIMENT 2.—Dog H25 was an adult, male mongrel bulldog in good condition, weighing 12.4 kg. March 31, a complete series of functional tests was performed. April 1, the phenoltetrachlorphthalein test was repeated as an additional control. April 3, under ether anesthesia and using aseptic technic, a cholecystectomy was performed and the common duct doubly ligated and sectioned between clamps. The following day the dog was definitely jaundiced, extremely ill, and scarcely able to stand. There was bile in the urine.

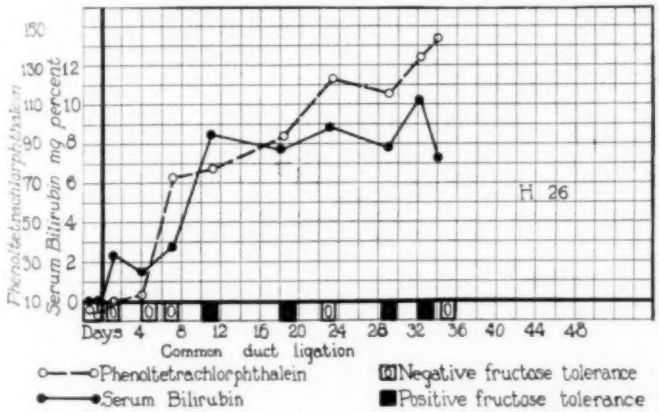

Fig. 1 (Dog H26).—Changes in serum bilirubin, phenoltetrachlorphthalein and fructose tolerance tests following ligation of the common bile duct.

Functional studies were made (Fig. 3). April 5, the animal was somewhat better. The stools were very light in color. April 8, the animal was much improved and was eating well, but thereafter emaciation constantly increased, and there were icterus and anorexia (Table 2). The dog was found dead in the cage fifty-five days after the operation.

At necropsy the mucous membranes, sclerae, subcutaneous fat and linings of the heart and blood vessels were deeply tinged with bile. There was no free fluid in the peritoneal cavity and no evidence of peritonitis. The liver was shrunken and dark, weighing only 212 gm., and showed marked resistance on section. Both the extrahepatic and the intrahepatic bile passages were markedly dilated and filled with dark, viscid bile. The kidneys were swollen, and the cortex was bile stained.

Microscopic examination of the liver (Fig. 4) disclosed that the normal architecture was not disturbed, although there was considerable fibrous tissue thickening around the branches of the hepatic ducts. The bile ducts were thickened and there was much surrounding round cell infiltration. Staining from bile was marked in the central portion of the lobule, the canaliculi being filled with pigment masses. The hepatic cells were small and atrophic. The

TABLE 1.—*Changes Observed Following*

Date	Time After Operation, Days	Weight, Kg.	Urine: Icterus*	Urine: Albumin*	Urine: Bile*	Urine: Casts*	Urine: Phenolsulphonephthalein, per Cent.	Hemoglobin, per Cent.	Blood Nitrogen Partition Mg., per Cent.: Nonprotein Nitrogen	Urea	Uric Acid	Creatinin	Amino Acid Nitrogen	Bile Pigments (Serum): Bile Index	Serum Bilirubin, Mg., per Cent.	Van den Bergh Direct Reaction
3/31/24	..	13.4	0	...	0	...	60	109	35	41	Low†	1.1	8.0	0	0.0	0
4/ 1/24	..	13.4	0	....	....	....	..	....	..	..	.....	....	....	..	....	..
4/ 4/24	1	12.7	Trace	2	0	0	..	107	..	22	Low†	1.3	...	..	2.3	0
4/ 7/24	4	11.7	1	0	0	0	..	108	..	24	Low†	1.3	6.8	..	1.7	+
4/10/24	7	11.3	2	0	0	0	40	108	..	21	Low†	1.4	...	34	3.9	+
4/14/24	11	10.5	2	...	..	...	..	..	25	25	Low†	0.9	8.3	78	9.5	+
4/21/24	18	10.3	2	2	0	..	..	91	31	40	Low†	1.7	8.0	57	8.9	+
4/26/24	23	10.3	....	....	....	....	50	....	30	17	Low†	1.2	8.2	68	9.9	+
5/ 2/24	29	10.1	+	2+	0	0	66	96	30	21	Low†	1.3	8.1	95	8.9	+
5/ 5/24	32	10.0	+	1+	0	0	..	98	31	21	Low†	1.5	9.5	91	11.1	+
5/ 7/24	34	9.1	2	2	0	..	..	103	70	116	Low†	1.4	9.8	80	8.3	+

* Graded on a basis of from 0 to 4.
† Too low to read.

TABLE 2.—*Changes Observed Following Ligation of*

Date	Time After Operation, Days	Weight, Kg.	Urine: Icterus*	Urine: Albumin*	Urine: Bile*	Urine: Casts*	Urine: Phenolsulphonephthalein, per Cent.	Hemoglobin, per Cent.	Blood Nitrogen Partition, Mg., per Cent.: Nonprotein Nitrogen	Urea	Uric Acid	Creatinin	Amino Acid Nitrogen	Bile Pigments (Serum): Bile Index	Serum Bilirubin, Mg., per Cent.	Van den Bergh Direct Reaction
3/31/24	..	12.4	0	0	0	...	50	97	33	24	Low†	1.3	8.6	0	0.0	0
4/ 1/24	..	....	....	....	....	....	..	....	..	..	.....	....	....	..	....	..
4/ 4/24	1	11.4	Trace	Trace	1	0	..	124	31	14	Low†	0.9	6.8	51	4.9	+
4/ 5/24	2	11.0	2	2	0	0	..	....	29	19	1.5	1.2	7.3	72	9.1	+
4/ 8/24	5	10.5	2	1	0	0	..	....	27	16	Low†	1.3	7.6	71	10.5	+
4/11/24	8	10.0	2	0	0	75	..	....	..	16	Low†	0.5	6.7	57	5.9	+
4/16/24	13	10.2	2	Trace	..	..	..	....	37	21	Low†	1.2	9.8	44	5.1	+
4/22/24	19	10.0	2	Trace	0	50	80	....	25	13	Low†	1.3	5.6	40	6.5	+
4/28/24	25	9.2	2	Trace	..	..	..	102	29	..	Low†	1.2	6.5	68	7.3	+
5/ 5/24	32	9.3	2	1	0	..	..	85	25	17	Low†	1.2	7.0	50	5.2	+
5/12/24	39	9.1	2	1+	0	..	..	....	30	24	Low†	1.2	8.5	75	8.5	+
5/20/24	47	8.2	2	1+	1	80	..	113	33	31	Low†	1.4	7.6	..	10.0	+
5/26/24	53	7.4	2	1+	0	..	..	104	40	37	Low†	1.2	9.5	..	9.0	+

* Graded on a basis of from 0 to 4.
† Too low to read.

TABLE 3.—*Changes Observed Following Ligation of the*

Date	Time After Operation, Days	Weight, Kg.	Urine: Albumin*	Urine: Bile*	Urine: Casts*	Urine: Phenolsulphonephthalein, per Cent.	Hemoglobin, per Cent.	Blood Nitrogen Partition, Mg., per Cent.: Nonprotein Nitrogen	Urea	Uric Acid	Creatinin	Amino Acid Nitrogen	Fragility Test, Percentage Sodium Chlorid: Initial Hemolysis	Complete Hemolysis
4/17/24	..	12.1	1	0	0	60	125	33	28	Low†	3.7	7.5	0.48	0.34
5/ 2/24	1	10.9	1	1	1	..	122	27	23	Low†	1.8	6.2	0.42	0.28
5/ 6/24	5	11.0	1	1	0	..	....	28	30	Low†	1.4	....	0.42	0.28
5/ 9/24	8	11.0	Trace	+	0	54	....	..	39	Low†	1.3	6.4	0.42	0.26
5/15/24	14	10.0	Trace	+	0	..	80	28	41	Low†	1.4	6.7	0.40	0.28
5/16/24	15	....	....	....	....	60	....	..	..	.....	....	....	.....	.....
5/18/24	17	10.7	Trace	+	0	..	....	27	42	Low†	1.3	7.2	.....	.....
5/20/24	19	....	....	....	....	..	65	..	..	.....	....	....	.....	.....
5/21/24	20	10.1	1	+	0	..	....	25	19	2.4	1.2	...	0.40	0.26
5/22/24	21	....	....	....	....	..	....	..	..	.....	....	....	.....	.....
5/23/24	22	10.5	Trace	+	0	60	65	22	21	Low†	0.9	7.2	0.44	0.24
5/24/24	23	....	....	....	....	..	....	..	..	.....	....	....	.....	.....
5/26/24	25	9.5	0	+	0	..	60	.	..	Low†	0.9	...	0.42	0.28
5/28/24	27	....	....	....	....	..	....	..	..	.....	....	....	.....	.....

* Graded on a basis of from 0 to 4.
† Too low to read.

Ligation of the Common Bile Duct (Dog H26)

Coagulation Factors					Fructose Tolerance, Blood Sugar, Mg., per Cent.					Phenoltetrachlorphthalein					
	Fibrin, Mg., per Cent.									Dye in Serum, per Cent.					
Calcium, Mg., per Cent.	Whole Blood	Plasma	Coagulation Time, Min.	Calcium Time, Minutes	Initial	15 Minutes	1 Hour	2 Hours	Change	5 Minutes	10 Minutes	15 Minutes	1 Hour	2 Hours	Dye in Urine, Mg.
10.6	[illegible]	620	4.5	3.0	117	126	145	116	28	4	1	1	..	..	Trace
....	[illegible]	.....	...	...	....	....	...	....	...	2	1	0	0	0	....
....	[illegible]	1,210	4.5	3.0	124	130	130	142	18	5	2	2	0	0	0.2
....	[illegible]	.....	...	...	237	167	123	...	—114	7	2	2	2	0	....
9.8	[illegible]	887	8.5	5.5	90	118	119	100	29	20	17	14	11	10	....
10.7	[illegible]	.....	9.5	7.5	100	107	121	136	36	24	16	13	13	13	4.5
....	[illegible]	908	10.0	5.0	97	138	118	110	41	32	24	23	15	11	3.7
11.0	[illegible]	1,505	12.0	5.0	109	130	118	115	20	35	31	27	20	20	....
....	[illegible]	1,100	8.0	8.5	98	120	135	124	37	30	30	30	25	11	1.1
10.8	[illegible]	975	9.0	7.5	100	149	149	115	49	44	30	24	24	23	0.9
10.9	[illegible]	780	12.0	6.0	80	88	82	79	8	40	25	23	25	20	....
10.4	[illegible]	1,175	15.0	16.0											

the Common Bile Duct and Cholecystectomy (Dog H25)

Coagulation Factors			Fructose Tolerance, Blood Sugar, Mg., per Cent.					Phenoltetrachlorphthalein					
Fibrin, Mg., per Cent.								Dye in Serum, per Cent.					
Calcium, Mg., per Cent.	Plasma	Initial	15 Minutes	1 Hour	2 Hours	Change	5 Minutes	10 Minutes	15 Minutes	1 Hour	2 Hours	Dye in Urine, Mg.
10.7	.....	100	110	135	110	35	4	2	1	0	0	0.5
....	1,015	...	...	...	...	...	6	5	0	0	0	....
....	1,355	123	130	147	120	24	10	12	5	6	6	0.2
....	.....	100	107	133	105	33	15	12	12	12	13	0.1
....	.....	80	85	100	107	27	12	10	12	8	8	4.2
....	.....	103	146	144	104	43	16	13	10	6	5	1.1
10.1	1,265	106	135	148	146	42	18	14	13	8	4	1.3
....	1,200	106	135	148	146	42	18	12	12	12	10	1.7
10.5	1,115	95	118	133	124	38	26	13	13	12	10	1.6
10.8	1,300	92	120	130	107	38	27	20	20	12	12	....
11.0	890	95	97	148	117	53	16	16	10	10	9	1.5
10.4	2,515	88	111	140	145	57	32	25	25	15	8	2.8
10.4	1,115	79	87	190	180	111	32	20	11	10	10	4.9
10.2	.....	83	87	125	137	54	22					

Common Bile Duct and Cholecystectomy (Dog H32)

Bile Pigments (Serum)			Coagulation Factors			Phenoltetrachlorphthalein						
				Fibrin, Mg., per Cent.		Dye in Serum, per Cent.						
Bile Index	Serum Bile Pigments, Mg., per 1 Cent.	Van den Bergh Direct Reaction	Calcium, Mg., per Cent.	Whole Blood	Serum	Hemocoonia	5 Minutes	10 Minutes	15 Minutes	1 Hour	2 Hours	Dye in Urine, Mg.	Remarks
7	0.0	0	10.7	578	1,100	++	4	3	2	Trace	0	Trace	Dog lively; no icterus
37	3.6	+	10.8	530	1,020	++	13	13	11	10	14	3.5	Dog quite sick
58	5.8	+	10.3	547	915	0	15	10	10	10	8	1.7	Icterus 1
45	4.8	+	10.9	541	875	0	15	7	6	6	7	1.8	Sick; tube feeding; icterus 1 to 2
85	12.5	+	10.3	518	745	0	8	7	7	7	6	1.2	
..	13.4	+	....	....	.....	..	..	..	..	..	..	....	
47	7.8	+	9.9	581	850	0	13	10	8	8	6	2.1	Gaining slightly
..	....	+	....	....	.....	..	..	..	..	..	..	....	Rubber T tube into common duct
30	2.4	+	9.8	450	585	+	6	5	3	3	2	0.1	Bile in stool
..	1.8	+	....	....	.....	..	..	..	..	..	..	....	
17	1.7	+	9.1	406	690	++	8	5	5	4	2	0.5	
11	1.5	+	....	....	.....	..	..	..	..	..	..	....	Tube obstructed
..	2.9	+	....	....	.....	+	15	10	8	7	3	1.9	No bile in stool
..	3.6	..	....	....	.....	0	..	..	..	..	..	....	Death

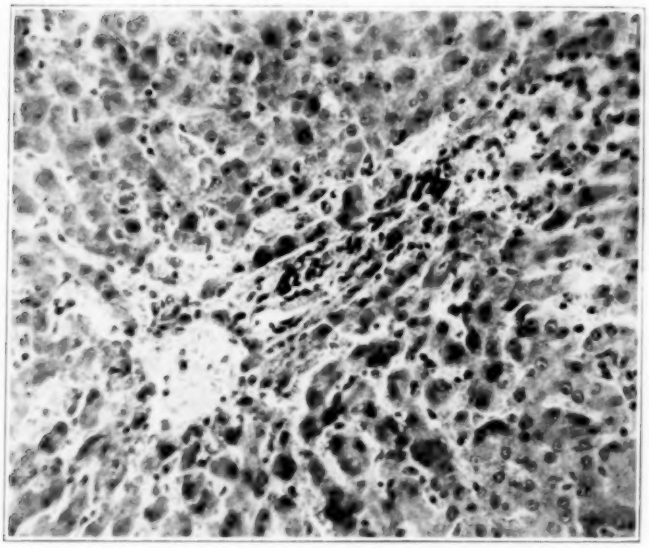

Fig. 2 (Dog H26).—Section of liver showing changes thirty-four days after ligation of common bile duct.

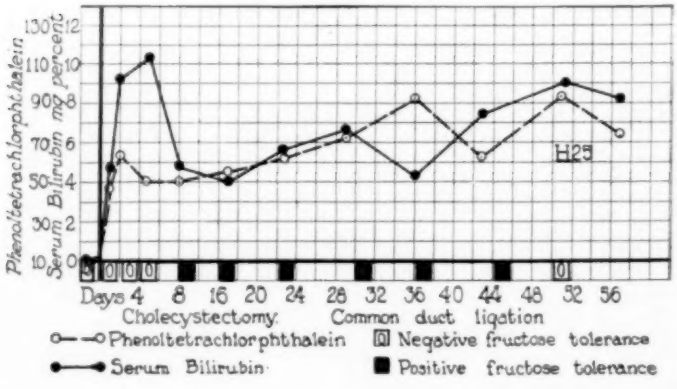

Fig. 3 (Dog H25).—Changes in serum bilirubin, phenoltetrachlorphthalein and fructose tolerance tests following ligation of common bile duct and removal of gallbladder.

sinusoids were dilated and there was a slight increase in the endothelial tissues. The changes were much more marked than in the preceding animal.

EXPERIMENT 3.—Dog H32 was an adult female, brown and white hound in good condition, weighing 12.1 kg. April 17, a complete series of functional tests was made (Fig. 5). May 1, under ether anesthesia and aseptic technic, cholecystectomy was performed and the common duct doubly ligated and sectioned between clamps. May 2, the animal was profoundly toxic, and the sclerae and mucous membranes were definitely icteric. May 6, the animal was somewhat better, but the icterus was unchanged. Thereafter there was progressive anorexia and loss of weight (Table 3). After May 15, the animal was fed daily a mixture of milk and corn syrup which checked the loss of weight but had no other apparent effect. May 20, a second operation was performed and an anastomosis made between the two portions of the common duct by means of a T-tube. At this time the extrahepatic bile ducts were greatly dilated and

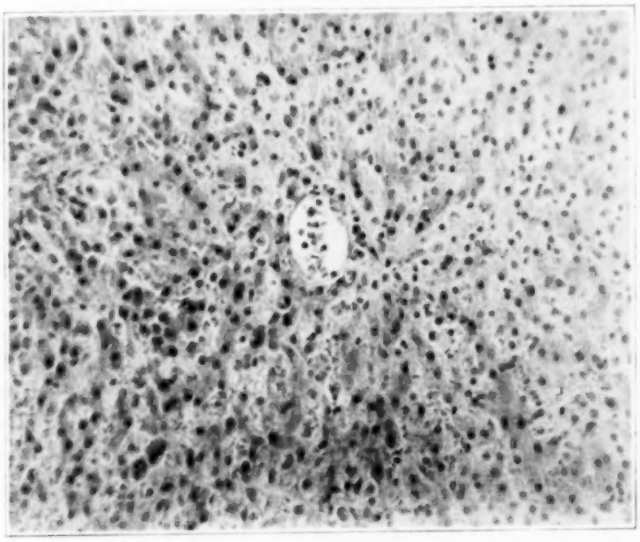

Fig. 4 (Dog H25).—Section of liver showing changes fifty-three days after ligation of common bile duct and removal of gallbladder.

thin-walled, and the operation was difficult. Following the operation there was a free drainage of bile from the T-tube, and the stools became darker in color, although they did not return to normal. May 26, six days after operation, drainage from the T-tube ceased and the dog's condition was obviously worse. May 27, tests of the stool for bile were negative. The animal became progressively worse and was found dead in its cage, May 28.

At necropsy the usual icteric staining was noted. The liver was deeply stained with bile and shrunken, and tough on section. The intrahepatic bile ducts were markedly dilated. The T-tube was kinked and the proximal end completely obstructed by calcareous material.

This experiment was of particular interest in that there was a definite decrease in the serum bilirubin and the degree of dye retention following operative relief of the obstruction. The drainage tube later became blocked, with consequent development of the changes characteristic of obstruction. These changes were similar to those seen clinically under similar circumstances.

DISCUSSION OF TESTS

Fructose Tolerance.—The changes in the fructose tolerance were studied by the technic of Bodansky.[2] The dogs were given 3 gm. of sugar for each kilogram of body weight, and the blood sugar determined fifteen minutes, one hour and two hours later by the method of Folin and Wu. In forty tests on normal animals the blood sugar increased from 10 to 20 mg. per cent. over the initial fasting blood sugar level. No rise greater than 35 mg. per cent. was observed in normal animals, and we have followed Bodansky in accepting this as the maximal normal value.

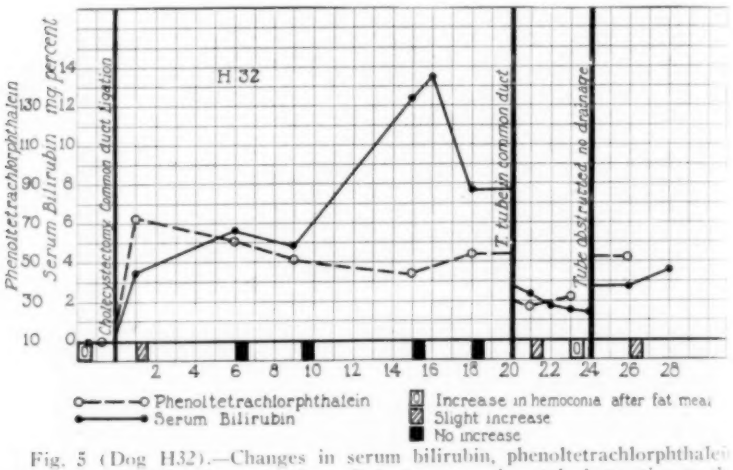

Fig. 5 (Dog H32).—Changes in serum bilirubin, phenoltetrachlorphthalei and hemoconia following operative relief of an experimental obstruction to th common bile duct.

Postoperative hyperglycemia made the interpretation of fructos tolerance tests difficult the first day after operation. A definite reduction in the carbohydrate tolerance was first observed from the second to the eleventh day after ligation of the common bile duct. There was no significant difference between the two series of experiments. Usually the reaction became positive about the sixth day and remained so until the death of the animal. Rises in the blood sugar of 40 mg. per cent. or more over the initial fasting level were the rule, and in some instances the initial blood sugar value was doubled. During the latter portion of the postoperative course, fructose tolerance occasionally was normal, but such responses apparently were accidental, since the reaction subsequently became positive. In two instances the fructose tolerance was

2. Bodansky, Meyer: Fructose, Glucose and Galactose Tolerance in Dogs, J. Biol. Chem. **56**:387-393 (June) 1923.

estimated on the day of death. In both the fasting blood sugar level was low, and no appreciable rise followed the administration of fructose.

The constancy of the changes observed in the fructose tolerance tests following the production of obstructive jaundice may well be interpreted as evidence of disturbance in the glycogenic activity of the liver. It is not necessary to consider the possibility of an associated pancreatic disturbance or diabetes mellitus in experimental animals, as it is in patients with obstructive jaundice. At the same time, the changes in this test cannot be interpreted as absolutely specific. In certain normal animals whose blood sugar during fasting was low, a rise of more than 50 mg. followed the ingestion of fructose. Such tests are difficult of evaluation since a definite hyperglycemia did not develop. Also, both in fasting animals and in those on a ketogenic diet, occasional positive results were obtained with maximal blood sugar values considerably above the normal limits.

Blood Sugar Level.—The rôle of the liver in the maintenance of the blood sugar level has been fully established by many investigators. In these experiments hyperglycemia was frequently observed on the day following operation, and it was ascribed to the operative procedure. After the induction of obstruction and the development of icterus, the blood sugar level during fasting usually was within the normal limits. In some animals a moderate terminal hypoglycemia was noted, a finding in accord with those of Isaac,[3] Williamson and Mann [4] and others, who made this observation in other forms of injury to the liver, especially in experimental phosphorus and chloroform poisoning.

Nitrogen Partition in the Blood.—Complete studies of the nonprotein nitrogenous constituents of the blood were made on each test day. No characteristic differences were noted between the results in the two series of experiments. The blood urea revealed the most consistent and characteristic changes of all the nitrogenous constituents studied. In general there was a definite fall following the development of jaundice. The decrease involved both the relative and absolute values for urea, while the total nonprotein nitrogen was less affected. This is well shown in Table 1. Shortly before death a sharp rise in the blood urea was noted as an antemortem phenomenon. These changes in the blood urea are of extreme interest, for Morgulis and Edwards [5] found that fasting alone

3. Isaac, S.: Theoretisches und Klinisches zur Stellung der Lävulose im Stoffwechsel, Med. Klin. **2**:1207-1210, 1920.

4. Williamson, C. S., and Mann, F. C.: Studies on the Physiology of the Liver, V, The Hepatic Factor in Chloroform and Phosphorus Poisoning, Am. J. Physiol. **65**:267-276 (July) 1923.

5. Morgulis, Sergius, and Edwards, A. C.: Chemical Changes in the Blood During Fasting and Subsequent Refeeding; Experiments on Dogs, Am. J. Physiol. **68**:477-498 (May) 1924.

caused an increase in the blood urea. Yanagi [6] and others have reported that the blood urea is decreased in patients with marked jaundice. Rowntree, Marshall and Chesney [7] showed a decrease in the percentage of the urea to total nonprotein nitrogen, and Bollman, Mann and Magath [8] have demonstrated that hepatectomy produces marked interference with the formation of urea in the body, as evidenced by low values for the blood urea. Nevertheless, it should be pointed out that, while the blood urea in general is decreased following the production of experimental jaundice, the values still fall within the lower limits of normal.

In only two instances did determinable quantities of a substance giving the color reactions of uric acid appear in the blood. Both instances represented isolated observations apparently without general significance. This again serves to emphasize the difference between the reactions in these animals and in those in which the liver has been completely removed, in whose blood Mann has emphasized the regular appearance of uric acid.

Bile Pigments.—Bilirubin is not a normal constituent of dog's blood or at least it is not present in appreciable quantities. From the standpoint of renal excretion it may be considered a non-threshold substance and any free pigment in the plasma is promptly excreted in the urine. With the production of obstructive jaundice the usual pathway of excretion is blocked, and bilirubin appears in the blood in amounts greater than the kidneys can excrete. On the appearance of bilirubin in the blood stream the serum first exhibits an indirect van den Bergh [9] reaction. This reaction later becomes diphasic and finally direct, as the amount of pigment increases.

Only traces of bilirubin were found in the blood twenty-four hours after ligation of the common duct. The van den Bergh reaction usually became direct after from forty-eight to seventy-two hours, at which time the serum contained from 2 to 4 mg. per cent. of bilirubin.

Clinical evidences of obstruction developed more slowly, and frank icterus usually did not appear until the third or fourth day after operation. Bile pigments were not found in the urine before the second day. In this series of animals, the amount of bile retention increased pro-

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6. Yanagi, K.: A New Colorimetric Method for the Determination of Urea with Urease, J. A. M. A. **82**:1169-1171 (April 12) 1924.

7. Rowntree, L. G.; Marshall, E. K., Jr., and Chesney, A. M.: Studies in Liver Function, Tr. A. Am. Phys. **29**:586-625, 1914.

8. Bollman, J. L.; Mann, F. C., and Magath, T. B.: Studies on the Physiology of the Liver, VIII, Effect of Total Removal of the Liver on the Formation of Urea, Am. J. Physiol. **69**:371-392 (July) 1924.

9. Van den Bergh, A. A. H.: Der Gallenfarbstoff im Blute, Leiden, van Doesburgh, 1918, **8**.

gressively until the second or third week; thereafter the serum bilirubin values were constant, aside from slight daily fluctuations.

In animals with cholecystectomy, besides ligation of the common duct, jaundice developed much more rapidly than in those with simple obstruction. In two experiments an indirect van den Bergh reaction was first obtained thirty minutes after ligation of the common duct. This reaction later became diphasic. One and one-half hours after ligation of the common duct and removal of the gallbladder, the direct reaction was obtained. The serum at this time contained 0.3 mg. per cent. of bilirubin. At the end of four hours, the serum bilirubin was 2.2 mg. per cent. Twenty-four hours after operation the serum contained from 3 to 5 mg. per cent. of bilirubin. The urine contained large amounts of bile pigments, and the sclerae and mucous membranes usually had a definite icteric tinge. The amounts of bilirubin in the serum of the animals in

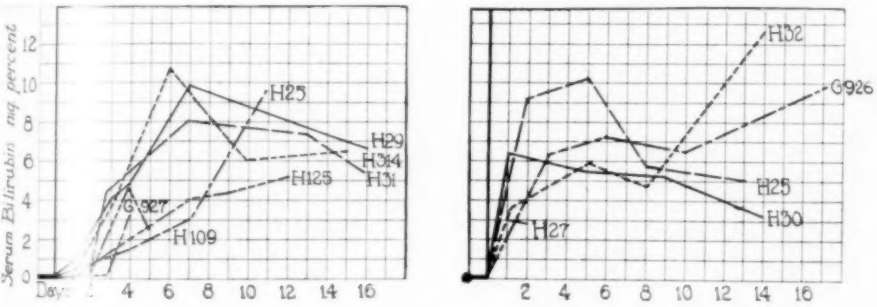

Fig. 6.—Effect of presence or absence of the gallbladder on changes in serum bilirubin following ligation of common bile duct. Left: without cholecystectomy; right: with cholecystectomy.

this group usually rose steadily during the first week, when a transient decrease occurred, with a subsequent rise to the final level (Fig. 6).

The clinical evidence of icterus increased somewhat as the obstruction continued, although the serum bilirubin was fairly constant during the latter portion of the dog's life. During this period there was little, if any, difference between the animals of the two series of experiments. In both groups the serum bilirubin varied between 5 and 10 mg. per cent. on the average, and no rise greater than 13.5 mg. per cent. was noted. In this respect the experimental observations differ from the clinical, for while the serum bilirubin was markedly increased in these dogs, it did not approach the excessive amounts occasionally observed in jaundiced patients.

Fasting alone may occasionally cause the appearance of bilirubin in the urine of normal dogs. However, in none of the control animals was it possible to demonstrate the presence of a bilirubinemia.

The Hemoconia Test of Brulé.—The rôle of bile acids in fat metabolism has been discussed at length by Brulé,[10] who considers these acids essential for the absorption of fat from the intestines. The estimation of ultramicroscopic blood fat particles (hemoconia) after a fat meal was carried out according to his method in two animals. Before operation both showed the normal increase of hemoconia over the control specimen taken during fasting. When biliary obstruction was well established, no increase in hemoconia was noted in the ten tests performed on these two animals. Connection between the bile passages and the intestine was reestablished in one (Experiment 3). Thereafter the blood fat particles increased normally following the fat meal. A few days later the tube became obstructed and the test again became positive. These findings are in keeping with the views of Brulé, as he asserts that the saturation of intestinal mucosa with bile pigments may be sufficient to give a positive test for stercobilin in the stool even in the presence of well established obstruction. For this reason it would appear that the test for hemoconia may be somewhat more accurate than the simple stool examination for bile.

Coagulation Factors.—The delay in the coagulation time of the blood is a well known clinical phenomenon in cases of obstructive jaundice. It has recently been studied by Walters,[11] who has given calcium chloride intravenously to reduce the coagulation time and thus combat the tendency to hemorrhage following surgical procedures in such cases. The coagulation and calcium time of the venous blood was studied in all animals by the method of Lee and White,[12] who have pointed out that both the coagulation time and the calcium time were greatly prolonged in the presence of demonstrable icterus and remained so until death. The normal coagulation time of dog blood by this method varies between four and seven minutes.

Following the production of obstruction, the usual coagulation time varied between eight and twelve minutes, although the maximal value was fifteen minutes. In general there was a fairly close parallelism between the degree of bile retention and the coagulation time, although in some animals a spontaneous reduction in the coagulation time was noted late in the progress of the condition. The total calcium content of the serum did not vary from the normal following the development of jaundice.

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10. Brulé, Marcel: Recherches sur les ictères: les rétentions biliaries par insuffisance hépatique, Paris, Masson et Cie, 1922, **13.**

1. Walters, Waltman: Preoperative Preparation of Patients with Obstructive Jaundice, Surg., Gynec. & Obst. **33**:651-656 (Dec.) 1921.

12. Lee, R. I., and White, P. D.: A Clinical Study of the Coagulation Time of Blood, Am. J. M. Sc. **145**:495-503, 1913.

Blood fibrin determinations were made by the method of Foster and Whipple.[13] A sharp postoperative rise was noted in all animals with a gradual return to normal for several days. Thereafter values approaching the upper limits of normal were the rule; occasional high values were observed, but in no instance was there a definite decrease in the fibrin. No direct relationship between the coagulation time and the fibrin content of the blood was observed.

Fragility Studies.—The resistance of red blood corpuscles to hypotonic salt solutions, measured by the method of Giffin and Sanford,[14] was increased materially in two animals after the induction of biliary obstruction. Hemolysis in normal animals began in solutions of about 0.44 per cent., and was complete in solutions of from 0.3 to 0.32 per cent. In

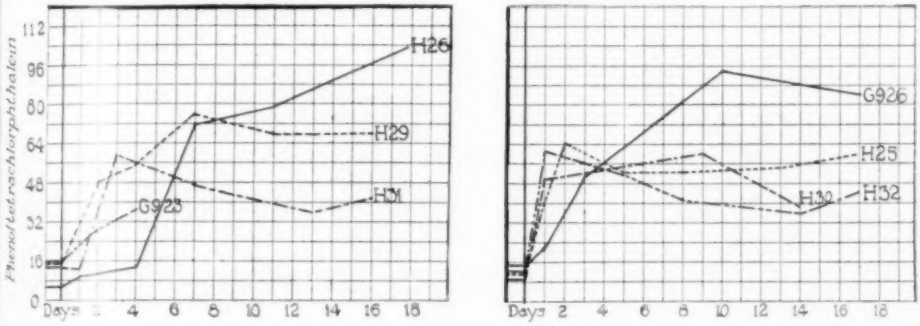

Fig. 7.—Effect of presence or absence of the gallbladder on development of phenoltetrachlorphthalein retention after ligation of common bile duct. Left: without cholecystectomy; right: with cholecystectomy.

the presence of bilirubinemia, dilutions as low as from 0.24 to 0.26 per cent. were required for complete hemolysis. This decreased tendency to hemolysis after the onset of jaundice was further evidenced by the appearance of the serum. Before operation it was difficult to obtain blood serum entirely free from hemoglobin, but as soon as the bilirubinemia was well advanced, perfectly clear specimens were the rule. Shortly before death, however, hemolysis was often noted.

Anemia was not a striking feature in any instance although there was a steady fall in the erythrocytes, as measured by the hematocrit, and the hemoglobin showed a slight decline. These findings were to be expected in view of the repeated bleedings to which the animals were subjected.

13. Foster, D. P., and Whipple, G. H.: Blood Fibrin Studies, IV, Fibrin Values Influenced by Cell Injury, Inflammation, Intoxication, Liver Injury and the Eck Fistula, Am. J. Physiol. **58**:407-431 (Jan.) 1921.

14. Giffin, H. Z., and Sanford, A. H.: Clinical Observations Concerning the Fragility of Erythrocytes, J. Lab. & Clin. Med. **4**:465-478 (May) 1919.

The Widal Hemoclastic Crisis.—Widal [15] has described a postalimentary leukopenia as one phase of what he terms "the hemoclastic crisis." He considers this leukopenia after a protein meal as evidence of hepatic insufficiency. The test was performed on three dogs with jaundice of long duration. The animals showed changes in the other laboratory tests, but the changes in the hemoclastic crisis were not characteristic (Table 4). The test was performed on two other animals before and after operation. Following the obstruction to the common duct, the two dogs showed a slight, but not characteristic leukopenia. All the animals with obstruction showed a high initial leukocyte count with considerable variation in successive counts; the variations made it difficult to ascribe small changes to the effect of the protein meal, and the interpretation of the tests was correspondingly difficult. Our results have led us to question the practical value of this test, at least in experimental work such as this.

TABLE 4.—*Widal Hemoclastic Crisis*

Dog	Duration of Obstruction, Days	Leukocyte Count				
			Time After Taking Milk			
		Fasting	0.5 Hour	1 Hour	1.5 Hours	2 Hours
G 926	14	8,800	7,200	7,600	10,200	11,100
H 26	12	15,900	11,600	15,500	19,800	20,500
H 25	12	20,800	21,600	27,400	32,600	30,000
H 32	0	10,500	10,300	13,600	16,300	19,800
	2	17,400	21,500	23,200	18,800	26,600
	7	19,200	18,800	18,600	19,200	15,200
	15	38,000	33,500	33,300	41,300	37,900
H 31	0	11,500	9,900	11,200	11,800	13,500
	3	21,900	21,700	20,700	21,800	20,400
	10	51,800	48,800	53,000	47,000	55,700

Phenoltetrachlorphthalein.—The original test of Rowntree, Hurwitz and Bloomfield [16] could not be applied in the study of obstructive jaundice as it was based on the measurement of the amount of dye excreted in the stools. Rosenthal [17] has since modified the test by substituting the measurement of the degree of the retention of dye in the blood for the study of the excretion in the bile. He found that phenoltetrachlorphthalein retention did not occur in experimental obstruction of the common duct. However, his observations on animals were confined to the first three days after the production of biliary obstruction.

15. Widal, Fernand; Abrami, Pierre; and Iancovesco, N.: L'épreuve de l'hémoclasie digestive dans l'étude de l'insuffisance hépatique, Presse méd. **2**:893-899, 1920.

16. Rowntree, L. G.; Hurwitz, S. H., and Bloomfield, A. L.: An Experimental and Clinical Study of the Value of Phenoltetrachlorphthalein as a Test for Hepatic Function, Bull. Johns Hopkins Hosp. **24**:327-342, 1913.

17. Rosenthal, S. M.: An Improved Method for Using Phenoltetrachlorphthalein as a Liver Function Test, J. Pharm. & Exper. Therap. **19**:385-391 (June) 1922.

Our animals were observed for a longer period, and definite changes associated with the development of icterus were present.

On account of the rapid disappearance of the dye from dog's blood, we used a dose of 10 mg. for each kilogram of body weight, twice the amount used for patients. In forty determinations on thirty-five normal animals we found that the greater part of the dye disappeared in fifteen minutes: the usual readings being between 6 and 8 per cent. after five minutes, 3 and 5 per cent. after ten minutes, and 3 per cent. or less after fifteen minutes. Traces of dye were found in blood specimens drawn one hour after its administration, but the two-hour specimens contained no dye. In normal animals an average of less than 1 mg. of dye was found in two-hour urine specimens.

We have compared the results of different tests on the basis of the sum of the dye readings obtained in the five specimens of blood taken in each test: that is, five, ten, fifteen, sixty and 120 minutes after the injection of the dye. In normal animals the total varies between ten and twenty, with an average of sixteen. This is an arbitrary method of comparison, but has been the most satisfactory for routine use since it is more convenient than the area method of Lamson,[18] and is a more sensitive index than the individual test, used clinically by us.

No retention of phenoltetrachlorphthalein in the blood stream of the dogs was observed until the second or third day following the ligation of the common bile duct. The development of distinct dye retention usually coincided with the first definite appearance of bile in the blood, both occurring from forty-eight to seventy-two hours after operation. Thereafter the amount of retention gradually increased, the maximal amount being obtained from the second to the fourth week. At this time, the sum of the readings varied between 40 and 60 per cent. on the average, while as much as 25 per cent. of the dye injected was present in the serum two hours afterwards. In general a gradually increasing serum bilirubin and dye retention were found, the two running an approximately parallel course until the death of the animal.

If cholecystectomy and ligation of the common bile duct were performed, dye retention was found twenty-four hours after operation. Here, too, a close parallelism with the amount of serum bilirubin was observed, the direct van den Bergh reaction and distinct dye retention appearing at the same time (Fig. 7). During the period immediately following operation these animals were, in general, much more affected by their biliary obstruction than those in the first group. Tests made at the end of the first week and during the second week usually showed a fall in serum bilirubin and a decrease in the degree of dye retention.

18. Lamson, P. D.; Gardner, G. H.; Gustafson, R. K.; Maire, E. D.; McLean, A. J., and Wells, H. S.: The Pharmacology and Toxicology of Carbon Tetrachlorid, J. Pharm. & Exper. Therap. **22**:215-288 (Nov.) 1923.

Later a secondary rise in both bilirubin and phenoltetrachlorphthalein retention was observed, the curve tending to remain stationary after the third week. The animals in this group lived somewhat longer and were in better condition than those in the first group, once they had become adjusted to their altered conditions and the effect of the bile retention. The amount of dye in the two-hour specimens of urine, in general, ran parallel to the degree of dye retention in the blood.

COMMENT

The morphologic changes in the liver due to long standing biliary obstruction and resultant jaundice are well known. The characteristic pathologic changes recently have been described in detail by Ogata,[19] MacCallum,[20], Bell,[21], Flynn [22] and others. No less definite are the functional disturbances evidenced by some of the tests studied by us. Certain tests failed to show clean cut changes due to the production of obstruction. This may imply either that such tests are not specific, or that the pathologic disturbances did not produce functional alterations sufficient to permit of their demonstration by these tests.

While it is known that the coagulation time of the blood is prolonged in cases of obstructive jaundice, the physiologic mechanism determining this delay is not known. The fibrin and the total calcium content of the serum are not deficient. The Widal hemoclastic crisis is not well adapted for use under the experimental conditions in our series, and the results did not correspond with the changes in the other tests. The Brulé hemoconia test, on the other hand, shows the presence or absence of bile salts in the intestines; and while it indicates obstruction in the biliary passages, it does not refer directly to the activity of the liver.

Theoretically, the most desirable test for the functional efficiency of the liver would be one that would indicate disturbances in the metabolic activity of that organ. Apart from the difficulty of securing a test specifically measuring the participation of the liver in protein or carbohydrate metabolism, one must also consider the large factor of safety present under normal conditions. The greater portion of the organ may be experimentally removed or destroyed without interfering with the well-being of the animal.

19. Ogata, Tomosaburo: Beiträge zur experimentell erzeugten Lebercirrhose und zur Pathogenese des Ikterus mit spezieller Berücksichtigung den Gallenkapillaren bei der Unterbindung des Ductus choledochus und der Ikterogenvergiftung, Beitr. z. path. Anat. u. z. allg. Path. **55**:236-314, 1913.

20. MacCallum, W. G.: A Textbook of Pathology, Ed. 2, Philadelphia, W. B. Saunders Company, 1920, p. 330.

21. Bell, L. P.: A Study of the Pathologic Conditions Encountered During and Following the Relief of Experimental Obstructive Jaundice Compared with Similar Pathologic Conditions in Man, Papers Mayo Foundation and University of Minnesota Medical School, 1921-1922, **2**:24-32.

22. Flynn, M. R.: Personal communication to the authors.

The decrease in the blood urea following the experimental production of biliary obstruction is definite though not marked. In view of the experiments of Bollman, Mann and Magath, these changes may be considered significant although they are not sufficiently well marked to be clinically applicable.

In cases of toxic injury from phosphorus, chloroform or hydrazin, changes in carbohydrate tolerance parallel the apparent response of the experimental animal. In obstructive jaundice similar changes in the fructose tolerance are obtained, indicating a failure of the organism to assimilate this form of carbohydrate. We believe, therefore, that fructose tolerance tests may be of value in experimental studies such as this, although we have pointed out elsewhere the difficulties in their clinical use.

The changes in the bilirubin content of the serum after the induction of jaundice are characteristic. Emphasis should be placed on the differences noted in the two groups of animals, the development of jaundice being delayed in those with an intact gallbladder. Mann and Bollman have previously pointed out the more rapid development of bilirubinemia in dogs following cholecystectomy, ligation of the cystic duct, or cholecystitis of chemical origin. With Rous and McMaster [23] they have shown that an intact gallbladder has the power of greatly concentrating the bile: this physiologic function of the organ suffices to delay the development of any increase in intraductal pressure and also postpone toxic hepatic injury due to bile retention.[24] On the other hand, removal of the gallbladder at the time of the ligation of the common duct prevents this concentration of the bile; the pressure within the hepatic duct rapidly rises, and there is a resorption of bile with a consequent rapid development of bilirubinemia and clinical icterus. The quantitative determination of the serum bilirubin by the method of van den Bergh is of the greatest value in the demonstration and study of these changes.

Much is still to be learned concerning the fate of phenoltetrachlorphthalein after its intravenous injection. If there is obstruction, the possibility of its accumulation in the biliary passages with subsequent resorption must be considered, although all the dye leaves the blood stream within a few hours, regardless of the state of the liver. No dye was found in the bile passages of these animals, although they had received repeated doses during the period of their obstruction. Small amounts of phenoltetrachlorphthalein are excreted in the urine, but the greater portion of the dye retained in the organism must have been

23. Rous, Peyton; and McMaster, P. D.: The Concentrating Activity of the Gallbladder, J. Exper. Med. **34**:47-73 (July) 1921.

24. Mann, F. C.: A Physiologic Consideration of the Gallbladder, J. A. M. A. **83**:829-832 (Sept. 13) 1924. Mann. F. C., and Bollman, J. L.: The Relation of the Gallbladder to the Development of Jaundice Following Obstruction of the Common Bile Duct, J. Lab. & Clin. Med. **10**:540-543, 1925.

destroyed, as there was no evidence of its accumulation in the tissues. Kendall [25] has shown that the closely allied phenolsulphonephthalein may be destroyed in this way. We have found that phenoltetrachlorphthalein is rapidly destroyed when incubated with ground liver or muscle. It is probable that a part of the phenoltetrachlorphthalein is destroyed in the body and that organs other than the liver may remove some of the dye from the blood stream. These factors are of minor importance, however, and do not militate against the use of the test, for the deviations from normal observed in animals with obstructive jaundice are characteristic and striking.

Following the production of biliary obstruction there is a close parallelism in the changes in the phenoltetrachlorphthalein test and the increase in the serum bilirubin. If the gallbladder is intact, a departure from the normal is not observed for a period of from forty-eight to seventy-two hours. Dye retention first appears with the development of a bilirubinemia. Thereafter the two tests show corresponding variations. If the gallbladder is removed at the time the common duct is ligated, dye retention will appear within twenty-four hours, coinciding with the early development of jaundice in animals of this group. The changes in the degree of dye retention during the initial period of obstruction apparently are directly determined by the extent of the bile retention. Since this is determined by the presence or absence of the gallbladder, we believe that the concentrating activity of this organ has only an indirect effect on the excretion of the dye.

Following the operative relief of the obstruction and reestablishment of biliary drainage, there is a decrease in the amount of bilirubin in the serum and the degree of dye retention (Experiment 3). While the changes are not so striking as those seen clinically after the relief of common duct obstruction, they nevertheless serve to emphasize further the close correlation in jaundice between the degree of bile retention and the retention of phenoltetrachlorphthalein. It is difficult to escape the conclusion that the two phenomena are directly related, and that dye retention is an index to the toxic effect of the retained bile.

Conclusions regarding the physiologic activity of the liver certainly should not be based solely on studies such as this. The changes indicated by certain hepatic functional tests in experimental obstructive jaundice appear to be significant, especially since they are of aid in determining the relative value of the various tests under controlled conditions, and furnish an experimental background for the interpretation of the deviations observed clinically.

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25. Kendall, E. C.: The Fate of Phenolsulphonephthalein When Injected Into the Animal Organism; Factors Other Than the Kidney Influencing Its "Retention"; Preliminary Report, J. A. M. A. **68**:343-345 (Feb. 3) 1917.

SUMMARY

A comparative study was made of certain tests for hepatic function in experimental obstructive jaundice. The changes observed in animals with simple ligation of the common duct were contrasted with those observed in animals with cholecystectomy and ligation of the common duct. In the presence of the gallbladder, the intoxication was less severe and the onset of icterus delayed. The development of jaundice did not cause changes in the blood sugar level during fasting, although fructose tolerance tests became positive, usually after the sixth day. There was usually a fall in the blood urea level, although terminal renal insufficiency later caused an antemortem rise in the blood urea. The serum bilirubin, determined by the quantitative method of van den Bergh, afforded a simple and accurate means of studying the degree of bile retention and the progress of the icterus. The coagulation time of the blood was prolonged, although the fibrin content was increased and the serum calcium was not changed. The phenoltetrachlorphthalein test in this condition showed dye retention in the blood stream that closely paralleled the degree of bile retention.

Book Reviews

PRACTICAL LECTURES: DELIVERED UNDER THE AUSPICES OF THE MEDICAL SOCIETY OF THE COUNTY OF KINGS, BROOKLYN, NEW YORK (1923-1924 Series). Pp. 484; 135 illustrations. Price, $5.50. New York: Paul B. Hoeber, 1925.

The centennial of the Medical Society of the County of Kings, Brooklyn, New York, was marked by a series of public lectures on practical subjects for general practitioners. These lectures on a wide variety of subjects make up the subject matter of this volume, which is profusely illustrated. The lecturers were carefully selected and the lectures are of uniform excellence.

TUMORS OF THE SPINAL CORD. THE SYMPTOMS OF IRRITATION AND COMPRESSION OF THE SPINAL CORD AND NERVE ROOTS. PATHOLOGY, SYMPTOMATOLOGY, DIAGNOSIS AND TREATMENT. By CHARLES A. ELSBER, M.D., Professor of Neurological Surgery, Columbia University; Consultant in Neurological Surgery, Presbyterian Hospital; Attending Surgeon, Mount Sinai Hospital and Neurological Institute, New York City. Pp. 421, with 354 illustrations. Price, $10.00. New York: Paul B. Hoeber, 1925.

This is a monograph along large lines. Like those by Cushing on "The Pituitary Body" and "Tumors of the Nervous Acusticus," and by Frazier on "Surgery of the Spine and Spinal Cord," it sets another landmark in the advanced development of neurosurgery in America. The bulk of the book is made up of eighty-one case histories, arranged topographically and profusely illustrated with pictures of gross and microscopic lesions, sensory charts, roentgenograms and steps in the operative technic. Then follow chapters discussing the symptomatology, cerebrospinal fluid changes, pathology, diagnosis and treatment. That a depository of special and highly technical data of this kind is useful to the internist is well stated in the following paragraph from the author's preface:

"To recognize that a pain in the chest is not due to intrathoracic disease but to a spinal root irritation, to distinguish between symptoms due to intra-abdominal disease and root symptoms due to spinal disease, to understand the true significance of a brachial, intercostal or sciatic neuralgia, may be difficult and may tax the diagnostic acumen of the physician. The same statement applies to the differentiation of the symptoms of primary disease of the bladder or prostate gland from the rectal and vesical disturbances that occur in spinal disease. Not so rarely patients have been treated for long periods and been subjected to operative interference for supposed intra-abdominal or pelvic disease when the cause was in the spinal cord or nerve roots."

RECOVERY RECORD: FOR USE IN TUBERCULOSIS. By GERALD B. WEBB, M.D., and CHARLES T. RYDER, M.D., Colorado School of Tuberculosis, Colorado Springs, Colo. Second edition. Pp. 81, with 100 weekly record sheets. Price, $2.00. New York: Paul B. Hoeber, 1925.

This book was first published in 1923, and has been reviewed in this journal; this second edition is a first reprinting and not a revision, as stated by the publishers. The book has been of great aid to convalescent tuberculous patients because of the sound advice given in language an average layman can understand, and because of the excellent weekly progress record sheets for the use of the patients attached.